

LYSINE-VASOPRESSIN IN EARLY EXCISION OF BURNS

An Experimental Study on
the Effects on Blood Loss,
Hemodynamics and Renal
Function

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LYSINE-VASOPRESSIN IN EARLY EXCISION OF BURNS

An Experimental Study on the Effects on Blood

Loss, Hemodynamics and Renal Function

by

Einar Vernerström

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The present dissertation is based on the following publications, which will be referred to in the text by their Roman numerals.

- I THE EFFECTS OF LYSINE-VASOPRESSIN ON HEMODYNAMICS DURING EARLY POST BURN PERIOD IN PIGS. In collaboration with I. Ahlgren, K. F. Aronsen, & H. Koopmann. Acta Chir Scand 148, 491 - 497, 1982.
- II LYSINE-VASOPRESSIN IN EXCISIONAL TREATMENT OF BURNS IN PIGS. Decreased Blood Loss and Earlier Circulatory Recovery. In collaboration with I. Ahlgren, K. F. Aronsen, & B. Palmer. Acta Chir Scand in press.
- III EFFECTS OF VASOPRESSIN ON HEART FUNCTION AFTER BURN IN PIGS. Submitted to Acta Anaesthesiologica Scand
- IV EFFECTS OF LYSINE-VASOPRESSIN TREATMENT ON RENAL FUNCTION IN BURNED PIGS. In collaboration with I. Ahlgren & K. F. Aronsen. Accepted for publication in Scand J Plast Reconstr Surg.

The following abbreviations will be used:

BSA = body surface area

CBF = coronary blood flow

CO = cardiac output

CR = coronary resistance

ELVW = external left ventricular work

GFR = glomerular filtration rate

IU = international unit

LVP = lysine-vasopressin

MAP = mean arterial pressure

MCVP = mean central venous pressure

MPAOP = mean pulmonary artery occlusion pressure

MPAP = mean pulmonary artery pressure

S = serum

SV = stroke volume

SVR = systemic vascular resistance

U = urine

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INTRODUCTION

The treatment of large burns remains a major challenge. The early burn shock is characterized by decreased cardiac output and hypovolemia followed by severe functional disturbances and morphological lesions in parenchymatous organs. The course of the burn syndrome and its treatment has been extensively investigated experimentally and clinically during the past decades as reviewed by Moncrief (1973), Rudowski et al. (1976) and Artz, Moncrief & Pruitt (1979). There are, however, only few studies dealing with the distribution of cardiac output and organ perfusion. Thus, in guinea pigs submitted to a full thickness skin burn covering 70 per cent of the body surface area, Ferguson et al. (1977) found severe cardiac output reduction and changes in blood flow as follows: the brain, heart, adrenals and the hepatic artery received an increased fraction and thereby an adequate perfusion. In the spleen, gastrointestinal tract, muscle and bone, the cardiac output fraction was unchanged and the blood flow thus reduced to the same degree as the cardiac output. Finally, the pancreas, skin, and adipose tissues received decreased fractions, causing an extreme reduction of blood flow in these organs. Similar changes were found by Wetterlin & Björkman (1977) in studies of a 15 per cent third degree burn in mice.

Since its suggestion by Cope et al. (1947), early excision with grafting has gained an increasing acceptance for achieving burn wound closure in thermally injured patients (Haynes, 1969; Janzekovic, 1970; Burke, Bondoc & Quinby, 1976; MacMillan, 1978 a; Sörensen, 1979). Early excision is appealing because it removes nonviable tissue from the burn wound and decreases the problem of burn wound sepsis. Moreover, early excision could decrease the resorption of toxic substances, which impair metabolism by damaging the mitochondria (Kremer et al., 1979), depress the function of the reticuloendothelial system (Loegering, 1981), and impair the host defence for bacterial infection (Schoenenberger, 1975). Further, immediate grafting decreases the metabolic and nutritional demands. Thus, early excision with grafting favourably influences the pathophysiological events, shortens healing time and increases survival rate, at least in children (Burke et al., 1974; Quinby, Burke & Bondoc, 1981). Major blood loss from the excised area is, however, difficult to avoid, and may further strain an already seriously burn injured patient. Techniques which can decrease excisional blood loss are urgently needed (Baxter, 1979; Jurkiewicz, 1979).

Vasopressin, a powerful constrictor of cutaneous and mesenteric vessels as well as of other vascular beds, decreases cardiac output and heart rate and increases arterial blood pressure when given in pharmacological doses to normovolemic animals (Drapanas et al., 1961; Ericsson, 1971; Hays, 1980). During hypovolemia due to hemorrhage (Cort et al., 1968; Ericsson, 1971) or burn (Wetterlin & Björkman, 1977), however, vasopressin has been shown to increase cardiac output and blood flow to vital organs. In normovolemic awake men, Erwald & Wiechel (1978), found that low pharmacological doses of vasopressin caused a moderate decrease of cardiac output and high doses caused an initial increase followed by a decrease. The circulatory effects of lysine-vasopressin (LVP) may prove favourable during early excision of burns. In a preliminary study in piglets, infusion of LVP during burn treatment was found to decrease blood loss during excision of a standardized burn by approximately 50 % (Vernerström et al., 1981). Local injection of ornithine-8-vasopressin has been claimed to reduce blood loss during the removal of burn eschar in children, (Keogh, 1974), but no quantitative data were given.

Following extensive burns myocardial depressant factors are formed in the burned skin and released to the circulation, causing impaired myocardial contractility in several species (Merriam, 1962; Baxter et al., 1966; Raffa & Trunkey, 1978). Vasopressin in pharmacological doses causes circulatory depression by a) reflex vagal inhibition secondary to increased arterial blood pressure, b) a negative chronotropic effect mediated via the central nervous system, and c) a direct myocardial depressant effect (Corliss et al., 1968; Varma et al., 1969; Heyndrickx et al., 1976). In addition there are reports indicating cardiac dysrhythmia and myocardial ischemia during LVP-treatment (Slotnik & Teigland, 1951; Drapanas et al., 1962), but other studies have not confirmed these adverse effects (Ericsson, 1971; Erwald & Wiechel, 1978). There is no investigation available concerning the effects of LVP in vasoactive doses on heart function in burn treatment.

Large burns induce several pathophysiological changes; hypovolemia, low cardiac output, increased sympathetic activity, hypoxia, and acidosis, all of which influence renal function (Eklund et al., 1970). Decreased perfusion and increased adrenergic renal nervous activity might cause decreased glomerular filtration rate and increased tubular fluid reabsorption which might cause acute renal failure (Loew & Meng, 1976). Impaired renal function has even been suggested to be one of the main survival determinants after major burns (Cameron & Miller-Jones, 1967), but with adequate fluid replacement, acute renal failure is rare (Moncrief, 1973).

At physiological concentrations the principal effect of the antidiuretic hormone or vasopressin is increased tubular water reabsorption and thus antidiuresis (Hays, 1980). In pharmacological doses, however, the same hormone has been shown to increase saluresis and diuresis due either to intrarenal vascular adjustments leading to increased glomerular filtration rate and consequently a larger volume of primary urine (Yesberg et al., 1973), or as a direct effect on the tubular sodium transport mechanism (Kurtzman et al., 1975). Considering the above facts it was decided to elucidate the renal excretory effects of LVP-infusion during burn treatment.

AIMS OF THE STUDY

The purpose of the present investigation was to study the effects of lysine-vasopressin treatment in pigs subjected to a standardized burn with regard to:

1. Central hemodynamics (paper I and II)
2. Cardiac output distribution and organ blood flow (paper I and II)
3. Blood loss during and after excision (paper II)
4. Heart function (paper III)
5. Renal function (paper IV)

MATERIAL AND METHODS

The material consisted of forty-seven female piglets weighing 24 ± 2 kg (range 19 - 29 kg). All animals were anesthetized and subjected to circulatory monitoring (CO, MAP, MCVP, MPAP, MPAOP and HR). In group A - C the duration of the experiments was 4 hours and in groups D - F the duration was 24 hours. The groups were defined as follows:

Anesthesia group, (A); The animals were anesthetized only, (n = 6).

Burn group, (B); The piglets were subjected to the standardized full thickness skin burn, (n = 6).

Burn-LVP group, (C); The piglets were subjected to the standardized burn and treated with synthetic lysine-vasopressin, (LVP, Postacton^(R), Ferring Ltd, Malmö, Sweden) 0.2 IU/kg/hour as continuous infusion throughout the experiment, (n = 6).

Burn group, (D); Standardized burn and circulatory monitoring, (n = 6).

Burn-excision group, (E); Standardized burn treated with excision 5 hours after the burn, (n = 6).

Burn-LVP-excision group, (F); Standardized burn treated with LVP and excision 5 hours post-burn, (n = 6).

Dose-response group, (G); The animals were given incremental doses of LVP (0, 0.008, 0.04, 0.2 and 0.4 IU/kg/hour) and their hemodynamics and renal function were monitored, n = 7.

Two pigs were anesthetized for 24 hours in order to study the circulatory stability during anesthesia per se, and two were used for isotope methodological purposes.

The animals were deprived of food for at least 12 hours before the experiments but had free access to water.

The investigation was approved by the Committy for Experimental Research in Animals, University of Lund.

Preparation of animals

One week before the 24-hour burn experiments a polyethylene catheter was placed into the left atrium through a small thoracotomy for microsphere injection according to Ericsson (1971), under thiopentone $\text{-O}_2/\text{N}_2\text{O}$ -suxamethonium anesthesia. In the 4-hour experiments, the left atrial catheter insertion was done after anesthesia was induced for the burn study.

Anesthesia

Thiopentone sodium (Pentothal^(R), Abbott) 20 mg/kg was used for induction and the animals were orotracheally intubated and ventilated with 70 per cent nitrous oxide in oxygen by means of an Engström 300 respirator (LKB, Medical AB, Sweden). The minute volume was adjusted to maintain PaCO_2 between 4.5 and 5.5 kPa. During preparation additional thiopentone was given as needed. During a stabilization period of one hour before baseline circulatory measurements were done, thiopentone was infused at a rate of 8 mg/kg/hour, which was gradually reduced after burn. After 6 - 8 hours the infusion rate was reduced to 2 - 1 mg/kg/hour to maintain a steady and light anesthesia throughout the experiment.

Experimental procedure

A polyethylene catheter (ID 1.65 mm) was introduced into the abdominal aorta via one femoral artery for pressure recordings and blood sampling. A Swan-Ganz flow directed thermodilution catheter (model 93 A - 131 - 7 F, Edwards Laboratories, St. Ana Calif., USA) was placed into the pulmonary artery under fluoroscopic control via one femoral vein. Urine sampling was performed through a suprapubic cystostomi. The first circulatory measurements were made one hour after the preparation was completed when the heart rate and MAP were stable, and the ^{103}Ru -labeled microspheres were injected into the left atrium in groups A, B and C. The animals in group B and C were then submitted to a standardized burn and the hemodynamics were followed during 4 hours in all groups. Two hours after the burn ^{141}Ce -tagged microspheres were given and after 4 hours ^{46}Sc -labeled microspheres were injected. In groups D, E and F, ^{85}Sr -tagged microspheres were used before burn, and ^{46}Sc -labeled microspheres 24 hours after burn. In paper II, all groups were submitted to the standardized burn and circulatory monitoring for 24 hours. The pigs in group E and F underwent excision of the burned area 5 hours after the burn. When the experiments were completed, the piglets were sacrificed and autopsied. Organs and tissues were removed, weighed and their radioactivity was measured.

Thermal injury

The pigs were subjected to a standardized full thickness skin burn using metal stamps (70 x 100 mm), heated to 150°C and applied to the shaved back and sides of the pig for 15 seconds (one stamp/kg body weight). The burn covered approximately 33 per cent of the total body surface area (BSA).

Fluid treatment

A solution containing 100 mmol NaCl and 25 g glucose per litre was given in amounts corresponding to 2.4 ml/kg/% burn/24 hours.

LVP-treatment

Lysine-vasopressin (Postacton^(R), Ferring AB, Malmö) infusion of 0.2 IU/kg/hour was started 15 minutes after the burn in group C, and 30 minutes after the burn in group F, and continued during the rest of the experiment. In group G, LVP was given in incremental doses (0, 0.008, 0.04, 0.2 and 0.4 IU/kg/hour).

Excision

Excision was performed in groups E and F by débridement of all dead tissue until a freely bleeding surface of fat or muscle fascia was obtained. All excisions were performed by the same surgeon (B.P.), experienced in burn care. Neither surgeon nor assistant knew to which group the pigs belonged. At excision bleeding vessels were clamped and the number of clamps was registered. Gauze pads were used to remove blood. During the remaining time of the experiment the wound surface was covered with an artificial skin substitute Epigard^(R) (Parke Davis and Company, Detroit, Michigan, USA). The weight of the removed tissues was also noted.

Blood loss determination

Blood loss was determined by weighing gauze pads and coverings before and immediately after use.

Pressure recordings

Mean arterial pressure (MAP), mean central venous pressure (MCVP), mean pulmonary artery pressure (MPAP), and mean pulmonary artery occlusion pressure (MPAOP) were measured using a conventional transducer (EMT-34) connected to an amplifier (EMT-311) and recorded by an ink jet recorder (Mingograf - 800) (all equipment was from Siemens Elema, Stockholm, Sweden). The reference point for the pressure transducers was taken at a plane 5 cm dorsal to the sternal angle.

Cardiac output

A thermodilution technique was used to determine cardiac output (CO) (Ganz et al., 1971). The catheter was connected to a cardiac output computer (Model 9520, Edwards Laboratories) and the thermodilution curve was also recorded by a potentiometer recorder (Servogor RE-511 S, Goertz Electro, W. Germany). As thermal indicator 5 ml of 0 - 1⁰ C isotonic glucose solution was injected during 1 - 2 seconds into the inferior vena cava during expiration. Double CO determinations were performed both immediately before and after the microsphere injections. When CO was measured unrelated to measurements of regional blood flow, 3 separate recordings were made. The mean of these separate determinations was taken as the actual CO.

Microspheres

All microspheres used were made of an inert plastic material and measured 15 ± 1 microns in diameter. The specific gravity was 1.3, according to the manufacturers. In the experiments described in paper I, they were purchased from NEN-TRAC (New

England Nuclear, Boston, Massachusetts, USA) and labeled with either ^{103}Ru , ^{141}Ce or ^{46}Sc . In the experiments described in paper II the microspheres came from 3 M, St. Paul, Minnesota, USA, and were labeled with ^{85}Sr or ^{46}Sc . They were suspended in 10 ml dextran and to prevent aggregation, one drop of Tween 20 was added to each ampoule. Before injection the microspheres were mechanically agitated to ensure even distribution and were then administered with a 2 ml disposable syringe as a bolus through the catheter into the left atrium. The catheter was repeatedly flushed with saline. The radioactivity of the catheter was measured at the end of each experiment and found negligible. The number of microspheres injected ($0.8 - 2.0 \times 10^6$) was chosen to obtain good counting conditions and was related to their specific radioactivity. The total radioactivity of the microspheres given was determined as the differences between the activity of the syringes before and after the injection.

Measurement of radioactivity

The organs were divided in pieces weighing at most 100 g and the radioactivity was measured in a Marinelli Chamber with a 4 x 3 inch thallium activated sodium-iodide crystal placed 18 cm from the center of the specimen. The output from the detector was transmitted to a gamma spectrometer (Canberra Analyser 830 A, and a 816 A Multiplier) with window settings adjusted for optimal separation of the different radionuclides: 55 - 190 keV (^{141}Ce), 440 - 580 keV (^{85}Sr and ^{103}Ru), and 740 - 1240 keV (^{46}Sc).

Determination of CO distribution and organ blood flow

The fractional distribution of each of the isotopes used was calculated by dividing the activity recorded in each organ or tissue by the total activity of the isotope injected. The sum of the values found for the stomach, spleen, pancreas and the intestines was taken as the value for the preportal area, while total liver flow was defined as the sum of the splanchnic organs and a. hepatica. Carcass activity is taken as the difference between the sum of the organ activities and the total activity of the isotope injected. The blood flow to individual organs or vascular beds was calculated by multiplying the fractional value by the mean cardiac output determined immediately before and after injection of the microspheres.

Derived hemodynamic variables

The stroke volume was calculated by dividing cardiac output by the heart rate, as

measured from the aortic pulse recordings. The external left ventricular work was estimated as the mean pressure gradient from the left atrium to the aorta multiplied by the cardiac output. The systemic vascular resistance was calculated as the mean pressure gradient from the aorta to the vena cava, divided by the cardiac output. Coronary vascular resistance was calculated as the mean pressure gradient from the aorta to the vena cava, divided by coronary blood flow.

Laboratory analyses

Blood hemoglobin and hematocrit, serum albumin, and serum enzymes (alkaline phosphatase, aspartate-aminotransferase, alanine-aminotransferase, and gamma-glutamyl-transferase) were determined using standard methods (Laurell-Lundh-Nosslin, 1980). Serum and urine sodium concentrations and serum and urine potassium concentrations were determined by flame photometry and urine osmolality by the freezing point depression technique (Dorwart & Chalmers, 1975). Creatinine was determined by the Jaffé reaction (Bartels & Böhmer, 1971).

Glomerular filtration rate (GFR)

In the groups A - F, GFR was estimated by determining the endogenous creatinine clearance rate. In the LVP dose-response study (group G), GFR was estimated by measuring the clearance rate of ^{51}Cr -EDTA by a continuous infusion technique (Aurell & Ditzel, 1970).

Presentation of data

All results are expressed as the mean $\pm$ standard deviation. The limits for the significance of differences were determined, as appropriate, either by the Wilcoxon rank sum test or Wilcoxon's test for paired differences. Differences having p-values < 0.05 were regarded as significant.

DISCUSSION OF METHODS

Experimental animals

Domestic pigs were used because they are in many ways physiologically similar to man (Bustard, 1966; McClellan, 1968), and their skin has similarities to the human skin during normal conditions and also in thermal vulnerability and pathophysiological reactions to burn injury (Henriques & Moritz, 1947; Wachtel et al., 1977). They are also large enough to allow comprehensive circulatory monitoring and re-

peated blood collection without induction of hypovolemia.

Preparation of animals

Thoracotomy for insertion of the atrial catheter was tolerated well by all the animals. When the pigs in paper II were autopsied 6 - 8 days later, most animals showed small adhesions of the lung to the thoracic wound, but no signs of infection, pleural effusion or bleeding. The tip of the catheter was in all cases situated in the left atrium and no extravasated blood was found. After the insertions of the different catheters on the day of the main experiment, the pigs were allowed to stabilize during 1 hour before the circulatory measurements started. Preparative procedures therefore are regarded to have influenced minimally on the results obtained.

Anesthesia

This study was performed under thiopentone - O_2/N_2O anesthesia. To maintain a stable anesthesia and to minimize the effects on circulatory parameters, the animals were normoventilated and thiopentone was given as an infusion. In the control anesthetized pigs (I and II) only minor changes of CO, MAP and pulse rate were observed, indicating a circulatory steady state during the experiments.

Thermal injury

The burning technique used with high temperature and short exposure time was found suitable concerning reproducibility. The extent of the burn injury (33 per cent of B.S.A) was chosen to be moderately larger than those usually excised at a single operation in clinical practice (MacMillan, 1978 b; Jurkiewicz, 1979).

Fluid treatment

The total volume infused was 2.4 ml/kg/% burn/24 hours and the infusion rate adjusted to give half of this amount during the first 8 hours and half during the next 16 hours. The volume was chosen in the low range of commonly used burn resuscitation formulas (2 - 4 ml/kg/% burn/24 hours) as the treatment was started immediately after the injury tending to reduce fluid requirements (Pruitt, Jr., B. A., 1978). There is also less oedema formation in pig skin than in human skin (Moritz, 1947). Wachtel et al. (1977) found that 2 ml/kg/% burn/24 hours is sufficient for circulatory recovery in burned miniature swine.

Vasopressin treatment

Lysine-vasopressin was used because it is the pig's natural antidiuretic hormone.

It has also been widely used to treat upper gastrointestinal bleeding in clinical practice (Conn et al., 1975; Eiseman & Norton, 1977; Hays, 1980; Johnson et al., 1982).

Excisional procedure

The same surgeon performed all excisions using a cold knife to ensure a standardized operating technique. The depth of the burn injury was considered simple to determine as the damaged subcutaneous fat was darker than non-injured fat.

Cardiac output determination

A thermodilution technique was used because it permits repeated cardiac output measurements without influencing subsequent determinations. The possibility that microsphere injection could change the cardiac output was controlled by measuring cardiac output immediately before and after the microspheres were injected. Good correlation between thermodilution and the dye dilution technique has been shown (Ganz et al., 1971; Rosberg, 1978).

Determination of regional blood flow

The radioactive microsphere technique for studying regional blood flow was introduced by Rudolph and Heymann in 1967. The method utilizes the principle of measuring the distribution of an indicator during the first transit in the vascular system. As indicator, carbonized microspheres of a uniform size, labeled with different radionuclides, are used. The method allows for sequential determinations of regional blood flow in the same animal. The technique implies the following basic assumptions:

1. That microspheres are uniformly mixed with the blood and show the same rheology as red blood cells.

In this study the microspheres were injected into the left atrium. This has been shown to give complete mixing of the microspheres with the blood (Kaihara et al., 1968), and also to give reliable results when measuring coronary blood flow (Domenech et al., 1969). The specific gravity of the microspheres is slightly higher than that of whole blood but there is no evidence of preferential streaming (Rudolph & Heymann, 1967; Neutze et al., 1968). Good dispersion of microspheres in the abdominal aorta following atrial injection was indicated by excellent correlation between the radioactivity found in the left and right kidney in the present study as well as in several previous investigations in our laboratory (Ericsson, 1971; Ohlsson, 1971; Ahlgren 1976; and Rosberg, 1978).

2. That the microspheres are of uniform size and too large to pass through any capillary bed.

According to Wagner et al. (1969), microspheres large enough to be trapped in any capillary, but small enough to pass any open arteriovenous shunt should be regarded to represent the nutrient blood flow. Spheres passing through preportal shunts will be trapped in the liver (Ohlsson et al., 1970) and those passing systemic shunts in the lungs (Kaihara et al., 1968). Substantial systemic arterio-venous shunting of microspheres, 15 ± 5 microns in diameter, has been demonstrated in different animals (Kaihara et al., 1968; Ohlsson, 1971; Prakash et al., 1981). Thus, the radioactivity measured in the lungs in the present study represents both systemically shunted spheres and the bronchial artery flow. The lung fraction was, however, considerably lower in this investigation which might depend on a more uniform microsphere size (15 ± 1 micron in diameter according to manufacturers). The radioactivity found in the liver reflects the hepatic arterial blood flow but also to a minor extent, microspheres shunted in the gastrointestinal tract. Ohlsson (1971), found no significant difference in the liver uptake of simultaneously injected 15 ± 5 and 50 ± 10 micron spheres in anesthetized dogs. Since the used microspheres in this study were more uniform in size, the detected radioactivity in the liver was regarded as representative of the hepatic arterial flow.

3. That the microsphere injection has minimal effect on circulation.

It has been shown that up to 4×10^6 of 15 ± 5 micron spheres do not change coronary or general circulation (Fortuin et al., 1971). Repeated injections of differently labeled microspheres in the same animal do not change the distribution of blood flow according to Rudolph & Heymann (1967) and Kaihara et al., (1968). In the present investigation $0.8 - 2.0 \times 10^6$ spheres were injected. There were no changes in mean arterial blood pressure, heart rhythm or cardiac output due to the injections of microspheres.

4. That the radioactivity of each radionuclide can be measured with reliability and separated from others.

The statistical counting error of the technique and the geometric error depending on small variations in distance between the specimen and the crystal has been thoroughly evaluated by Ericsson (1971) and Ohlsson (1971). In one pig, spheres labeled with the three nuclides ^{141}Ce , ^{103}Ru , and ^{46}Sc were injected simultaneously. In another animal microspheres tagged with ^{85}Sr and ^{46}Sc were injected in the same way to establish that there was no systemic error between the measurement of

different radionuclides.

Fig. 1 demonstrates an excellent correlation between the cardiac output fraction obtained with ^{85}Sr and ^{46}Sc with the values for the individual organs close to the line of identity. Similar results were obtained in the pig that received three differently labeled microspheres. The result indicate that the method is reliable for blood flow measurements.

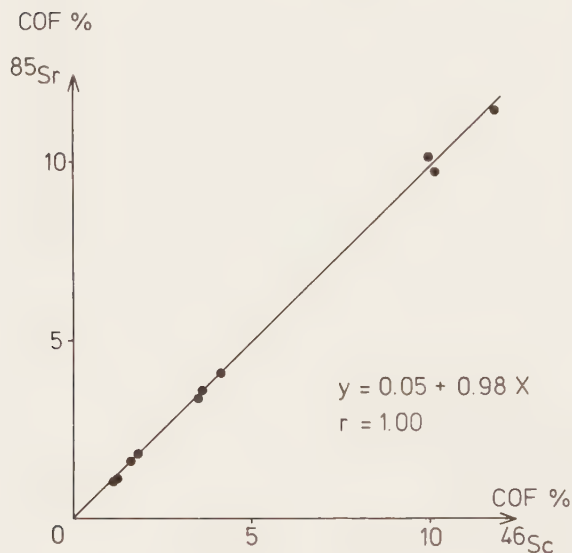


Figure 1. Comparison of the cardiac output fractions in the individual organs, expressed as per cent, obtained after a simultaneous injection of microspheres labeled with ^{85}Sr or ^{46}Sc .

Determination of glomerular filtration rate

This was performed by calculating the endogenous creatinine clearance rate in the animals in group A - F, because the method is simple, repeated 4-hour GFR values were calculated, and the bladder was catheterized allowing precise urine sampling. Further, as other radioactive isotopes were injected for measurement of regional blood flow, determination of GFR by the ^{51}Cr -EDTA clearance rate might have been disturbed. The former method has also been widely used clinically and found to give reliable values (Doolan et al., 1962). In the dose response study (group G, IV) not receiving other isotopes, ^{51}Cr -EDTA clearance was used to obtain better

accuracy (Brüchner-Mortensen et al., 1969).

RESULTS

Central hemodynamics

The animals tolerated the experimental procedure well. There were no significant changes in MPAP, MPAOP or MCVP in any of the groups. As can be seen in fig. 2, the hemodynamics were stable in the anesthesia group (A). Early after the burn injury

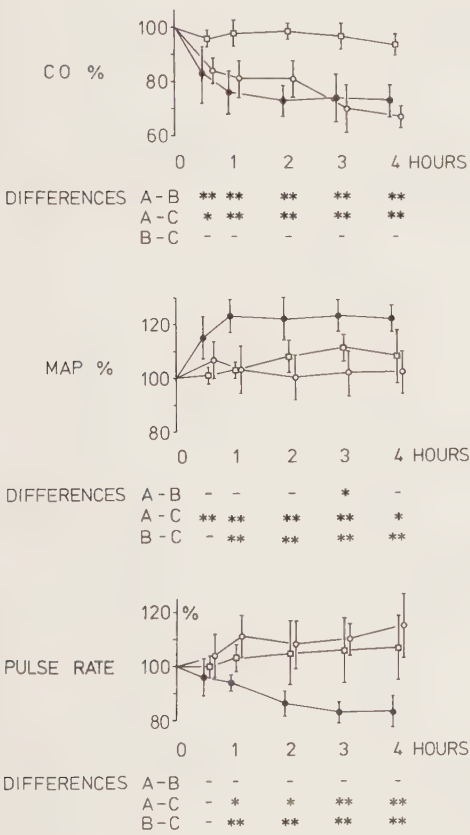


Figure 2. Cardiac output (CO), mean arterial pressure (MAP), and pulse rate given in per cent of baseline values. Anesthesia group (A) = □, burn group (B) = ○, and burn-lysine-vasopressin (LVP)-group (C) = ●. Differences between groups, * p < 0.05, and ** p < 0.01. Mean $\pm$ SD, n = 6 in all groups.

CO decreased approximately 30 per cent whether LVP-treatment was given or not and remained low for 24 hours in the conservatively treated pigs (group D), (fig. 2 and 3). After the excision, performed 5 hours after the burn, there was a gradual recovery of CO in group E and after 24 hours CO had reached 88 per cent of the pre burn value. Fig. 3 shows that the restitution of CO started earlier in the LVP-treated and excised group (F), and that at 8 hours post burn CO was significantly higher than in the pigs receiving fluid therapy only (group D). There was no significant differences between groups F and E.

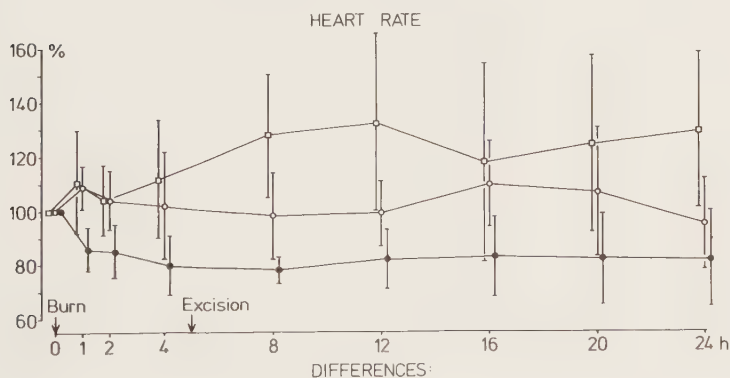
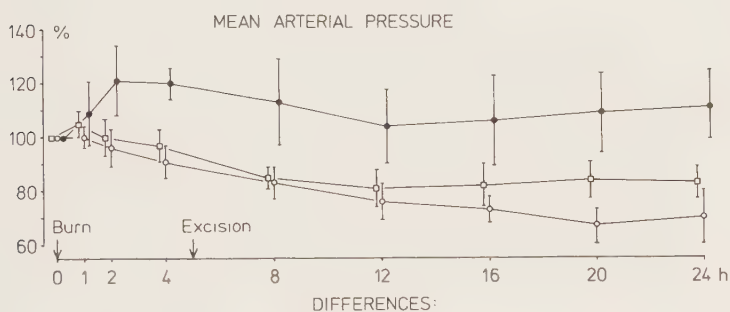
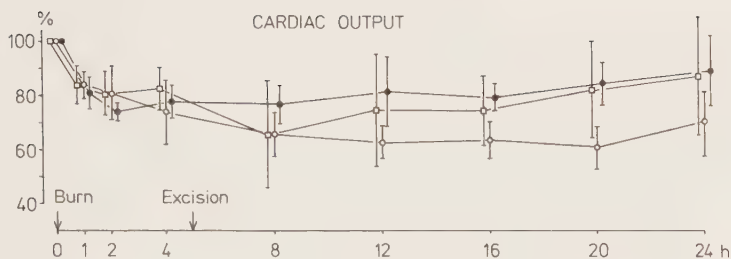
Early after the burn injury, MAP was only little changed (fig. 2) but later decreased about 30 per cent in the burned group (D). In the burn-excision group (E), the MAP reduction was less than in group D, and at the last three recordings MAP was significantly higher. In the LVP-treated groups (C and F) MAP was invariably increased and higher than in the other groups (fig. 2 and 3).

In the burn groups (B and D) heart rate was relatively stable. After excision pulse rate was more unstable in group E, and at 8, 12 and 24 hours it was significantly higher than in group D, see fig. 3. In the LVP-treated pigs (groups C and F), heart rate was decreased and was also significantly lower than in the other groups (fig. 2 and 3).

Regional blood flow

The results of the determination of CO fractional distribution and organ blood flow are presented in detail in tables I - VI (appendix). The regional blood flow remained unchanged during 4 hours of anesthesia (group A) apart from a decrease in lung flow and an increase in kidney perfusion (table I). Two hours after burn (group B), blood flow to the heart, lungs, pancreas, small intestine and skin was decreased. After 4 hours the decreased perfusion also included the large intestine, total liver and carcass (table II). In group B, 2 hours after burn, blood flow to the heart, small bowel, total liver, and kidneys was significantly lower as compared with the anesthesia group (fig. 4). In this figure, it can also

Figure 3. Cardiac output, mean arterial pressure, and heart rate given in per cent of pre-burn values (mean $\pm$ SD), n = 6 in all groups. Burn group (D) = o, burn-excision group (E) = □, burn-lysine-vasopressin (LVP)-group (F) = ●. Differences between groups, * p < 0.05, and ** p < 0.01.



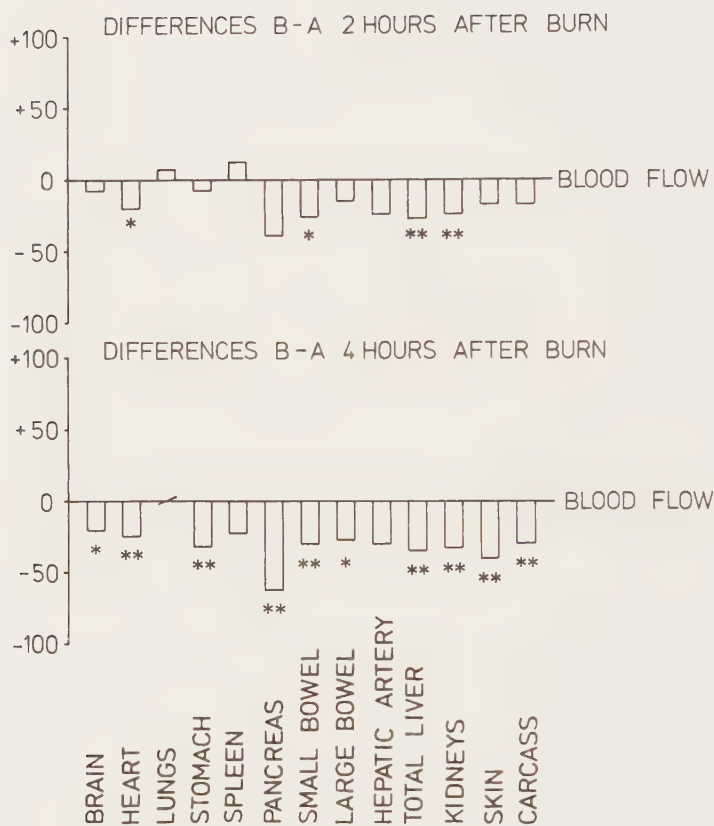


Figure 4. Differences in organ perfusion between burn group (B) and anesthesia group (A), after 2 and 4 hours given in per cent. * $p < 0.05$, and ** $p < 0.01$. The figure is derived from tables I and II.

be seen that after 4 hours, blood flow to most organs was lower in group B than in group A.

Blood flow to the heart, lungs, small intestine, and total liver remained low 24 hours after the burn (group D), while brain perfusion was moderately increased (table IV). In the burn-excision group (E) the regional perfusion was decreased to a slightly lesser degree (table V) 24 hours after burn, but there was no significant difference compared with group D.

In the burned and LVP-treated pigs (group C), the hepatic artery blood flow was markedly increased, but decreased to the heart, lungs, stomach, pancreas, small and large intestines, skin, kidneys, and carcass (table III), 2 and 4 hours after burn. When group C is compared with group B, it can be seen (fig. 5) that LVP induced significantly lower blood flow to the proximal gastrointestinal tract, skin and carcass, while the arterial liver flow was increased. After 24 hours, in the burned, LVP-treated and excised group (F), blood flow was increased to the brain and liver and remained low to the lungs, stomach, pancreas, small bowel and carcass and was unchanged to the other organs (table VI). When group F is compared with group D and E, fig. 6, demonstrates that LVP still causes lower blood flow to the proximal gastrointestinal tract and skin and markedly higher liver perfusion after 24 hours.

Blood loss

In group E, the blood loss during excision was 107 ± 39 ml/25 kg and after excision 39 ± 18 ml/25 kg. The number of clamps used was 28 ± 8 . The weight of the excised skin and subcutaneous tissue was 1058 ± 101 g/25 kg. During the excision in the LVP-treated group (F), blood loss was 41 ± 13 ml/25 kg and afterwards it was 9 ± 6 ml/25 kg. The blood loss in the group with LVP-treatment and excision (F) was significantly less than in the group with excision only (E). This applies to the loss during and after excision as well as to the total blood loss. The number of clamps was 22 ± 5 in group F and the excised tissue weighed 1023 ± 115 g/25 kg.

Values for hemoglobin and hematocrit increased in the burn group (D) during 24 hours, while there were no changes of these values in groups E and F. S-albumin decreased moderately in all groups. There were no apparent changes of importance of the S-enzymes in any of the groups. Further, there were no major differences between the groups in the abovementioned laboratory data (table 1).

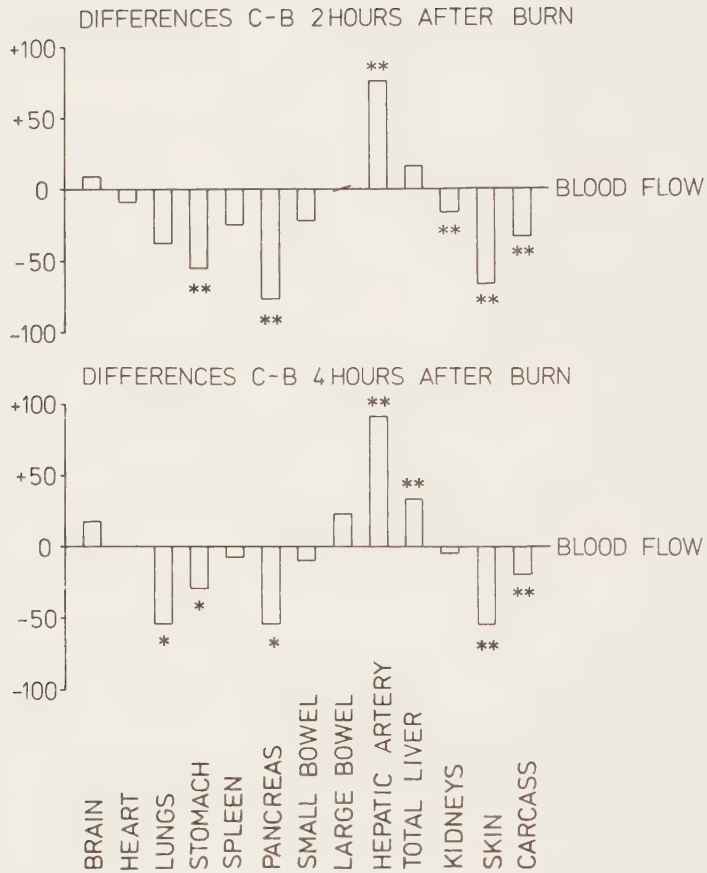


Figure 5. Differences in organ perfusion between the burn-LVP group (C) and burn group (B), after 2 and 4 hours given in per cent. * $p < 0.05$, and ** $p < 0.01$. The figure is derived from tables II and III.

Table 1. The values of different blood and serum laboratory investigations performed before burn and 24 hours after burn in the burn group (D), burn-excision group (E), and burn-LVP-excision group (F). Significant changes from the preburn values are denoted by underlined figures, $p < 0.05$, and differences between groups * $p < 0.05$, and ** $p < 0.01$.

Time (hours)	Group D		Group E		Group F	
	0	24	0	24	0	24
B-Hb (g/l)	93 ± 12	<u>106 ± 21</u>	89 ± 15	95 ± 17	90 ± 13	94 ± 11
B-Hkr (%)	31 ± 4	<u>34 ± 6</u>	30 ± 6	31 ± 7	31 ± 2	32 ± 4
S-alb (g/l)	31 ± 4	<u>24 ± 2</u>	30 ± 5	<u>25 ± 4</u>	27 ± 2	23 ± 1
S-sodium (mmol/l)	146 ± 5	144 ± 4	143 ± 3	145 ± 5	145 ± 5	141 ± 4
S-potassium (mmol/l)	4.2 ± 0.6	4.3 ± 0.3	4.0 ± 0.3	4.3 ± 0.3	4.0 ± 0.3	<u>3.8 ± 0.2</u> (D*, E*)
S-creatinine (mmol/l)	79 ± 17	<u>106 ± 20</u>	81 ± 13	88 ± 12	77 ± 7	78 ± 8 (D**)
S-ASAT (ukat/l)	$.53 \pm .13$	$.88 \pm .26$	$.78 \pm .20$	$.89 \pm .43$	$.44 \pm .17$	<u>$.67 \pm .21$</u>
S-ALAT (ukat/l)	$.75 \pm .22$	$.72 \pm .27$	$.81 \pm .20$	$.73 \pm .14$	$.58 \pm .11$	<u>$.49 \pm .07$</u> (E**)
S-ALP (ukat/l)	5.1 ± 1.9	5.0 ± 1.2	5.2 ± 2.1	6.0 ± 2.6	4.1 ± 1.1	<u>6.9 ± 3.1</u>
S-GT (ukat/l)	$.40 \pm .11$	$.29 \pm .03$	$.47 \pm .15$	$.30 \pm .06$	$.50 \pm .28$	<u>$.35 \pm .17$</u>

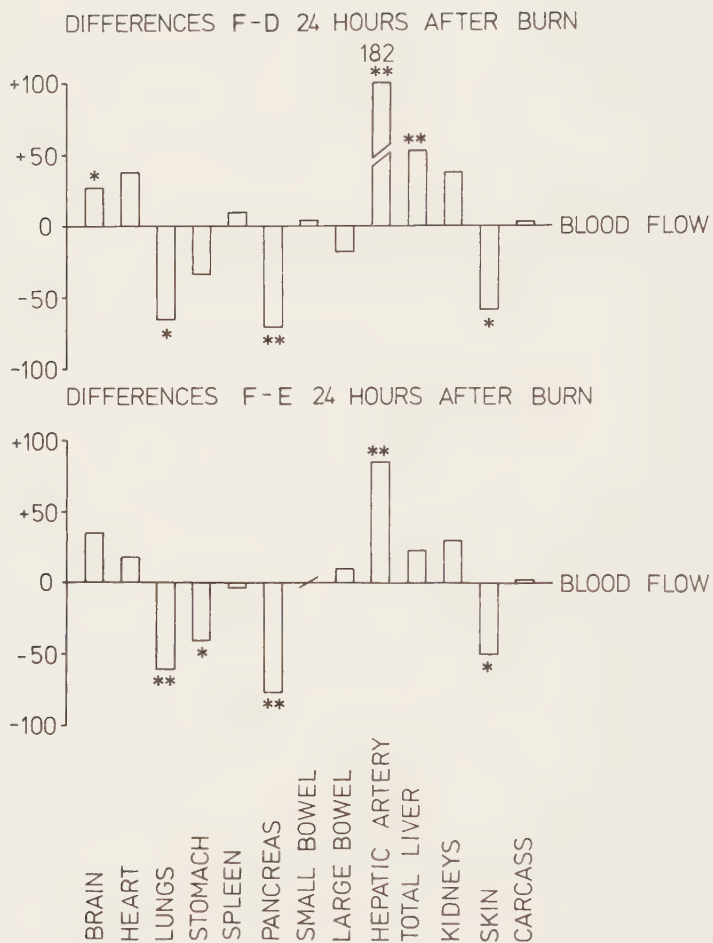


Figure 6. Differences in organ blood flow after 24 hours, between burn-LVP-excision group (F) and burn group (D), and between burn-LVP-excision group (F) and burn-excision group (E), given in per cent. * $p < 0.05$, and ** $p < 0.01$. The figure is derived from tables IV, V, and VI.

Cardiac function

In the anesthesia group (A) external left ventricular work remained unchanged during 4 hours (fig. 7), but decreased in the burn group (B) and was significantly lower than in group A. After 24 hours external left ventricular work was reduced by 52 per cent of the pre burn value (group D). In the burn-excision group (E) the decrease 24 hours after the burn amounted to 27 per cent.

LVP-treatment after burn led to a moderate decrease of external left ventricular work after 2 and 4 hours (group C). In the LVP-treated and excised group (F), however, external left ventricular work was restituted 24 hours after the burn and was significantly higher than in groups D and E (fig. 7).

The stroke volume was reduced at all determinations in groups B, D and E. Early after the burn, stroke volume was moderately decreased also in the LVP-treated animals (C). After 24 hours stroke volume was slightly increased in group F, and was significantly higher than in the other groups (D and E, fig 7). In the LVP-treated groups (C and F), there were significantly higher external left ventricular work ($p < 0.01$) related to coronary blood flow, than in the other groups with burns (B, D and E).

Systemic vascular resistance increased early after the burn (group B), and the increase was more pronounced during LVP-infusion (group C). After 24 hours systemic vascular resistance had returned to the pre burn level in groups D and E, but remained moderately increased in the burn-LVP-excision group, F, see fig. 7.

There were positive correlations between the individual values for coronary blood flow and external left ventricular work in all groups. Heart function, expressed as external left ventricular work in relation to pulmonary artery occlusion pressure, was depressed early after the burn regardless of whether LVP was given or not (groups B and C, fig. 8) but after 24 hours heart function was better in the LVP-treated and excised group (F) than in the other groups (D and E).

Renal function

Renal blood flow increased during 4 hours of anesthesia, but decreased early after the burn (groups B and C) and was significantly lower than in the anesthesia group (A, tables I - III). Renal blood flow was still moderately decreased 24 hours after the burn, (tables IV - VI). There were no significant differences

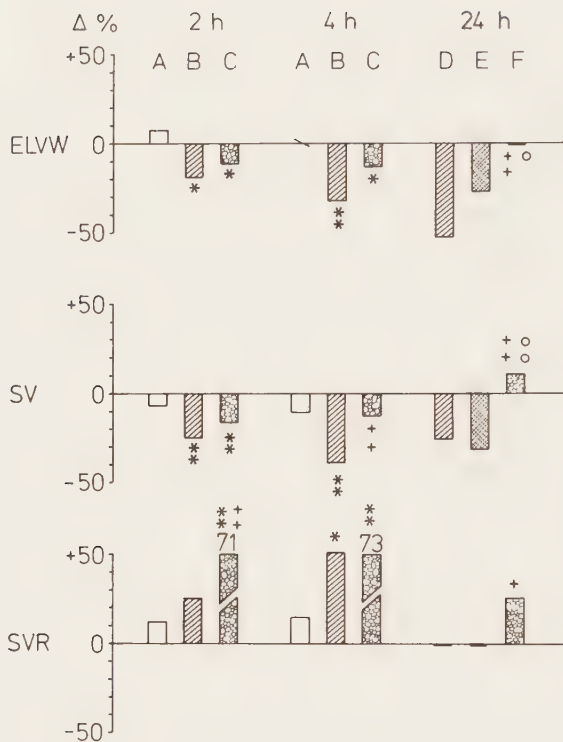


Figure 7. Percentage changes from pre-burn values of external left ventricular work (ELVW), stroke volume (SV), and systemic vascular resistance (SVR) in the different groups, A = anesthesia group, B and D = burn groups, C = burn-LVP group, E = burn-excision group and F = burn-LVP-excision group. Significant differences between A and B or C, * $p < 0.05$, and ** $p < 0.01$, between C and B or between F and D, + $p < 0.05$, and ++ $p < 0.01$, and between F and E, $^{\circ}$ $p < 0.05$, and $^{\circ\circ}$ $p < 0.01$.

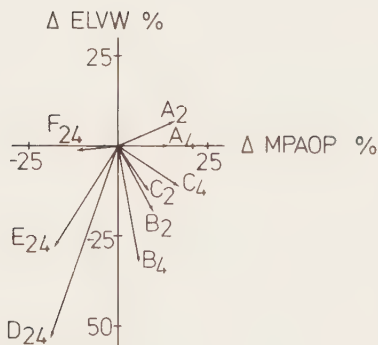


Figure 8. The relation between mean percentage changes in external left ventricular work (ELVW) and mean pulmonary artery occlusion pressure (MPAOP). A = anesthesia group, B = burn group, and C = burn-LVP group after 2 and 4 hours. D = burn group, E = burn-excision group, and F = burn-LVP-excision group after 24 hours.

between the groups D, E and F.

During 4 hours after the burn GFR was slightly lower in the burn group (B) than in the anesthesia group (A), but in the burn-LVP group (C) GFR was significantly higher than in group B (fig. 9). During the 24-hour experiments mean GFR was higher in the LVP-treated and excised group (F) compared with the other groups (D and E), but the differences were significant during only two periods (fig. 10).

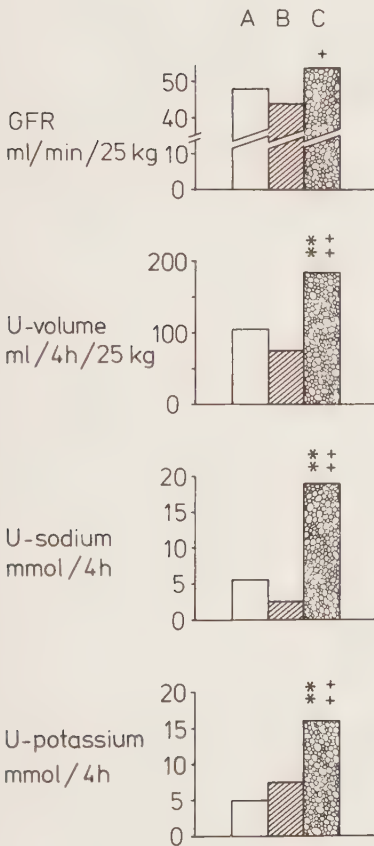


Figure 9. Mean values of glomerular filtration rate (GFR), U-volume, U-sodium and U-potassium in the anesthesia group (A), burn group (B), and burn-LVP-group (C), during 4 hours. Significant differences between C and A, * $p < 0.05$, and ** $p < 0.01$, and between C and B, + $p < 0.05$, and ++ $p < 0.01$.

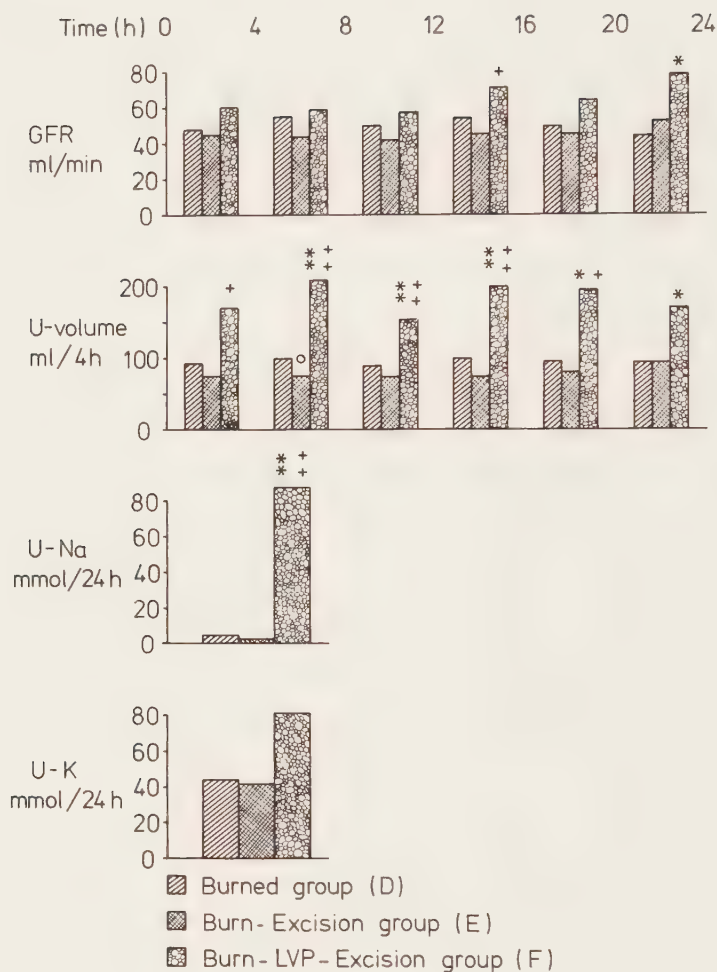


Figure 10. Mean values of glomerular filtration rate (GFR), and U-volume for each 4 hour period, and mean values for U-sodium and U-potassium during 24 hours. D = burn group, E = burn-excision group, and F = burn-LVP-excision group. Significant differences between E and D, ⁰ p < 0.05, between F and D, * p < 0.05 and ** p < 0.01, and between F and E, + p < 0.05, and ++ p < 0.01.

Diuresis was moderately smaller after the burn (group B) than in the anesthesia group (A), but in the burn-LVP group (C) it was significantly larger (fig. 9). The urine volume was markedly larger in the burn-LVP-excision group (F) than in the other groups (D and E) throughout the 24-hour study (fig. 10).

In the burn groups without LVP-treatment (B, D and E) there was low urinary sodium excretion (fig. 9 and 10) compared with the anesthesia group (A), while the potassium excretion was higher. In the burn groups treated by LVP (C and F) the sodium and potassium excretion were markedly larger. U-osmolality was lower (689 ± 75 mosm/kg) in group C than in group B (806 ± 51 mosm/kg, $p < 0.05$).

S-sodium remained unchanged in groups D, E and F during 24 hours (table 1) as did S-potassium except for a small decrease in group F. S-creatinine increased during the experiment in burn group (D) and was unchanged in groups E and F. S-creatinine was significantly lower in the burn-LVP-excision group (F) than in burn group (D) after 24 hours.

In the dose-response study group (G) cardiac output decreased significantly during the two highest doses of LVP (fig. 11) and MAP increased. GFR was significantly increased at the LVP-infusion rates 0.04 and 0.2 IU/kg/hour, but not at the lowest (0.008) or highest (0.4) LVP-doses (fig. 11). The U-volume was unchanged during the lowest LVP-dose, but with incremental LVP-doses the diuresis was markedly increased. The sodium excretion was significantly increased during all but the lowest LVP-dose, while the potassium excretion was increased for all doses (table 2). U-osmolality was decreased during the two highest LVP-doses. S-sodium was stable, S-potassium increased and S-creatinine decreased during the experiment (table 2).

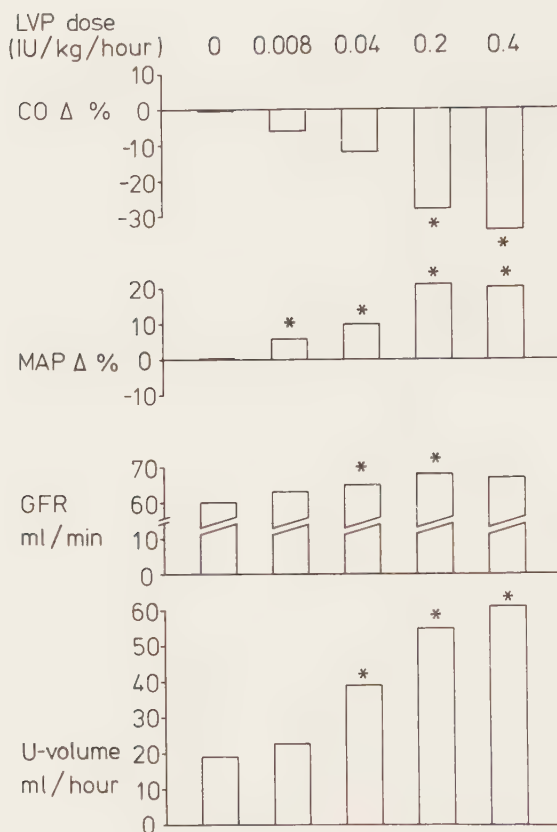


Figure 11. Mean percentage changes in cardiac output (CO), and mean arterial pressure (MAP). Mean glomerular filtration rate (GFR) and U-volume for the different lysine-vasopressin (LVP) doses in group G. Significant change from the baseline value, * $p < 0.05$.

Table 2. The values of sodium, potassium, and osmolality in urine and sodium, potassium, and creatinine in plasma for incremental doses of lysine-vasopressin (LVP) in group G. Significant changes from baseline values are denoted by underlined figures, $p < 0.05$.

LVP-dose (IU/kg/hour)	0	0.008	0.04	0.2	0.4
U-sodium (mmol/hour)	1.2 ± 0.6	1.2 ± 0.5	<u>4.3 ± 3.4</u>	<u>6.8 ± 5.9</u>	<u>9.1 ± 4.9</u>
U-potassium (mmol/hour)	1.3 ± 0.8	<u>2.5 ± 1.6</u>	<u>4.9 ± 1.3</u>	<u>7.5 ± 1.5</u>	<u>7.9 ± 2.0</u>
U-osmolality (mosm/l)	779 ± 78	798 ± 67	<u>722 ± 87</u>	<u>694 ± 98</u>	<u>696 ± 82</u>
S-sodium (mmol/l)	146 ± 4	145 ± 3	<u>146 ± 3</u>	145 ± 2	143 ± 3
S-potassium (mmol/l)	4.4 ± 0.4	4.5 ± 0.5	<u>4.8 ± 0.4</u>	<u>5.0 ± 0.4</u>	<u>5.1 ± 0.3</u>
S-creatinine (mmol/l)	92 ± 10	<u>89 ± 12</u>	<u>86 ± 10</u>	<u>86 ± 11</u>	<u>89 ± 8</u>

GENERAL DISCUSSION

The principle to surgically remove devitalized tissues has gained wide acceptance in burn care. The elimination of toxins by excision has been regarded as crucial to prevent impairment of host defence against infection and sepsis (Kremer et al. 1981; Echinard et al., 1982). The necrotic tissues, moreover, are excellent substrates for bacterial growth. They lead to continued losses of energy and fluid and prevent healing until they are removed and the burned area is covered with grafts (Arturson, 1980; Quinby et al., 1981). Early excision and grafting has also been shown to shorten hospitalization, improve functional and cosmetic results and in some studies reduce mortality (Janzekovic, 1970; Burke et al., 1976; Petersen et al., 1982). The blood loss during excision has, however, been one major factor limiting this procedure. The recommendation has been made that the excised area plus the donor site should not exceed 25 to 30 per cent of the total body surface area at one operation, to avoid excessive blood loss and surgical stress (MacMillan, 1978 b; Jurkiewicz, 1979). Therapeutic modalities reducing blood loss and operation time might also permit larger excisions in massively burned patients.

In the present study, LVP-treatment significantly decreased the blood loss both during and after burn excision. This substantial decrease can be ascribed to the potent peripheral vasoconstrictor effects of high-dosage vasopressin (Ericsson, 1971; Hays, 1980; I and II).

In clinical conditions, the excisional blood loss often amounts to more than the total circulating blood volume when the surgical area is of the above-mentioned extent (Haynes, 1969; Levine et al., 1975; Burke et al., 1976). In the present study on piglets, the blood loss in association with burn excision was 4 to 10 per cent of the total blood volume in the burn-excision piglets. The relatively small blood loss can be explained by the sparser skin vascularization in pig than in man (Montagna & Yun, 1964). Further the excision was performed 5 hours after burn, when the skin blood flow was low (I). Optimal conditions regarding blood loss has been found within 12 hours after burn in patients (Jougla et al., 1979).

LVP-induced vasoconstriction might jeopardize the survival of tissues with borderline viability and the healing of skin transplants. However, the punctate bleeding observed during the excision and the measured flow in adjacent skin,

which increased between the 4th and 24th hour after burn (I and II), demonstrated maintained perfusion. Vasoconstriction might also decrease edema formation. The similar weight of removed skin and subcutaneous tissue in the burn-excision and the burn-LVP-excision groups, indicated that the LVP-treatment did not influence the extent of the tissue damage.

Provided that the vessels of the human skin respond to LVP in the same way (Hays, 1980) as did those of the studied pigs, substantial decrease of blood loss during burn excision may be anticipated also in humans. This assumption has been supported by preliminary results in selected burn patients (Palmer, personal communication, 1982).

The immediate decrease in CO but relatively stable MAP and pulse rate found after burn, is a well known hemodynamic pattern early after burn injury (Moncrief, 1973). The decrease in CO after burn is mainly due to loss of fluid and plasma, and the formation of myocardial depressant factors (Raffa & Trunkey, 1978). The delayed CO recovery in the conservatively treated group (D) may, apart from the burn itself, be partly explained by the limited fluid therapy (2.4 ml/kg/% burn/24 hours), which is low in range of commonly used formulas in burn resuscitation (2 - 4 ml/kg/% burn/24 hours). In the clinical situation, low CO is not unusual 24 to 48 hours after burn despite conventional fluid treatment (Birke et al., 1958; Pruitt et al., 1971). Although the hemodynamics were stable in the control (anesthetized nonburned) piglets, some depressant effects on the compensatory circulation mechanisms after burn may have been induced by light anesthesia.

The excision performed 5 hours after burn, did not seem to involve hazardous strain on the burn-excision piglets. It seemed rather to promote earlier restitution of CO. MAP was also higher when excision had been performed, especially after 16 hours. The circulatory improvements could be explained by decreased loss of fluid and terminated resorption of toxic factors when the burned tissues were removed (Kremer et al., 1981; Quinby et al., 1981). The hemodynamic restitution, however, was to some extent counteracted by the blood loss during burn excision (range 54 - 154 g/25 kg). This loss was not replaced. The high pulse rate and its great variability in the burn-excision group (E), probably reflect the stress imposed on the circulatory homeostasis by the blood loss.

In the piglets treated by LVP (groups C and F), MAP increased and heart rate decreased (I and II). These are well known pharmacological effects of the hormone in normovolemia (Drapanas et al., 1961; Corliss et al., 1968; Ericsson, 1971).

The LVP-infusion was not associated with further post burn fall in CO as compared with other groups. Of greater interest was the CO recovery in the burn-LVP-excision group, which began after 4 hours. From 8 hours after burn, CO was significantly higher in this group than in the burn group, and remained so throughout the experiment.

The effect of vasopressin on CO has been shown to depend on the circulatory state before treatment. In normovolemic dogs, LVP reduces CO (Drapanas et al., 1961; Ericsson, 1971), but observations in man are nonconclusive (Erwald & Wiechel, 1978). Increased CO has been reported during vasopressin-treatment in dogs subjected to hemorrhagic hypovolemia (Cort et al., 1968; Ericsson, 1971) and in hypovolemic burned mice (Wetterlin & Björkman, 1977).

The favorable circulatory effects of vasopressin in shock of various kinds has been ascribed to constriction of the capacitance and mesenteric vessels, thereby increasing the central blood volume, MAP and subsequently CO (Cort et al., 1968). Selective microvascular constriction causing improved microcirculation, less edema formation and better venous return might also be responsible for the increased survival rate found after vasopressin treatment (Altura et al., 1965; Altura, 1973). Moreover, there is increasing evidence that vasopressin is an intrinsic, homeostatic regulator of vascular tone and thereby promotes microcirculatory blood flow and thus counteracts the development of decompensated shock (Altura, 1976, 1980). In addition, recent investigation has provided direct evidence that endogenous vasopressin promotes RES function in shock (Altura, 1980), which is another mechanism by which LVP might support circulatory homeostasis in compensated shock. In the present study, the CO recovery in the burn-LVP-excision group did not occur until after burn excision. Because of the administered fluid, the piglets were only moderately hypovolemic which explains the moderate circulatory changes. In moderate hypovolemia, the above CO-improving mechanisms probably are less important than in severe shock. The more stable circulation in the burn-LVP-excision group than in the burn-excision one, may also be explained in part by the reduced surgical blood loss.

After burn there were only minor changes in CO distribution, and the only significant difference between the burn group (B) and the anesthesia group (A), was the lower fraction into the pancreas. In the earlier investigations, more pronounced CO redistribution favouring vital organs were reported (Ferguson et al., 1977; Wetterlin & Björkman, 1977). This was probably due to a more extensive burn

without fluid therapy (Ferguson et al.), less intensive fluid therapy (Wetterlin & Björkman), or species differences. The small changes in CO fractional distribution led to moderately decreased organ perfusion largely in proportion to the reduced CO. The moderate changes of regional blood flow again suggests that the animals were in a fairly good circulatory state (I and II).

The changes in CO fractional distribution in burned pigs during LVP infusion, compared with burned animals without LVP, caused decreased systemic A-V shunting and decreased blood flow in the proximal gastrointestinal tract, skin and carcass. The perfusion of the brain, heart, spleen, large intestine and the kidneys were of the same order as in the other burn injured pigs, while the hepatic artery flow was greatly increased. The distribution of CO observed in this study is in accordance with earlier investigations performed in normovolemic animals (Ericsson, 1971; Schmid et al., 1974; Cort et al., 1975) reflecting the selective vasoconstriction in different organs.

The demonstrated increase in the hepatic artery flow, induced by LVP, caused a greater total liver perfusion than in the burn groups from the 4th hour post burn and remained throughout the 24 hour experiments. The liver is known to be of vital importance for the organism to prevent the development of irreversible burn shock (Arturson, 1961). The blood flow to the liver was decreased early after burn (I), which might interfere with its ability to eliminate toxic products (Allgöwer et al., 1973; Kremer et al., 1979; Kremer et al., 1981), and to meet increased metabolic demands (Arturson, 1961; Schoelmerich et al., 1979). The observed improvement of liver perfusion during LVP treatment, should be supportive for liver function. This assumption is supported by the vasopressin-induced enhancement of the reticular endothelial system function, found in bowel ischemia and hemorrhagic shock (Altura et al., 1976, 1980).

The changes in the analyzed serum enzymes were small in the 24-hour experiments (groups D, E and F) and were considered to be of little importance (II). Early post burn liver affection has been described in rats (Arturson, 1961; Arturson & Wallenius, 1963), and in pigs (Levine et al., 1974). The smallness of the changes in the present study may be explained by the administered fluid, containing glucose and electrolytes, and by the controlled ventilation which ensured good oxygenation and eliminated the breathing effort.

The increase in hemoglobin concentration and hematocrit in the burn group (D) is most likely the result of the sequestration of fluid and plasma known to occur

after burns (Pruitt et al., 1971), and may in part be due to the limited fluid replacement given. Hemoconcentration was counteracted in the excised groups (E and F), since the blood loss during excision was not replaced and there may have been less fluid loss after the removal of the burned tissues.

The increased systemic vascular resistance found early after burn (group B) can be explained by vasoconstriction due to increased sympathetic activity and to increased blood viscosity. The results are in accordance with those found by others in several species (Moncrief, 1966; Leape, 1971; Wetterlin, 1977; Aikawa et al., 1978). The vascular resistance was further increased during LVP infusion, caused by its peripheral vasoconstrictor effects.

Early after burn the external left ventricular work was decreased mainly due to the decreased CO. LVP treatment in group C, led to an increased blood pressure and a slightly higher external left ventricular work compared with the burn group (B). In the burn-LVP-excision group (F), left ventricular work reached its pre-burn level after 24 hours and was significantly higher than in the burn and the burn-excision groups (D and E). The restitution of external left ventricular work in group F was due to the recovered CO and to the moderately increase in arterial blood pressure.

In the LVP treated burn groups (C and F), there were significantly higher external left ventricular work related to coronary blood flow compared with the other burn groups (B, C and E). Therefore it might be suggested that LVP improved cardiac efficiency expressed as external cardiac work related to oxygen consumption. LVP is known to decrease the metabolic demands of the heart by reflex vagal inhibition secondary to increased blood pressure, a negative chronotropic effect mediated via the central nervous system, and a direct depressant effect on the myocardium (Varma et al., 1969; Heyndrickx et al., 1976; Cartheuser & Komarek, 1980). The negative chronotropic effect was evident in this study (I, II and III) and presumably also caused decreased metabolism in the heart. A decreased coronary blood flow during LVP infusion has also been attributed to primary coronary vasoconstriction, and by some investigators found to cause myocardial ischemia (Slotnik & Teigland, 1951; Drapanas et al., 1961). Corliss et al. (1968) found, however, that cardiac metabolism remained aerobic in spite of decreased coronary perfusion during vasopressin infusion concluding that the blood supply was sufficient for the metabolic demands in the myocardium. The different results could be explained by very large vasopressin doses given as a bolus in the earlier investigations, and also by

different experimental procedures.

A few hours after burn the left ventricular function (fig. 8), as reflected in changes in external left ventricular work and pulmonary artery occlusion pressure, was depressed whether LVP was given or not. The observed results are in accordance with the concept of myocardial depressant factors, formed in burned skin and possibly in the pancreas, circulating in burn plasma and impairing the myocardial function (Baxter et al., 1966; Rosenthal et al., 1972; Hakim, 1975; Raffa & Trunkey, 1978; Lefer, 1978). After 24 hours cardiac function had further deteriorated in the burn piglets but recovered in the burn-LVP-excision group. This could be explained by the combined favorable effects of decreased fluid loss and decreased toxin resorption after the excision, with minimal blood loss, and also the effects of LVP on circulation per se.

The renal function changes early post burn (group B) with lower blood flow and sodium excretion than in the control anesthetized pigs (group A), and fairly well preserved diuresis and GFR, have been reported in patients (O'Neill et al., 1967; Cameron & Miller-Jones, 1967). In the 24-hour experiments similar results were obtained in the burned non LVP treated piglets (groups D and E). Burn trauma causes increased sympathetic nervous system activity (Arturson, 1974) which contributes to the decreased kidney blood flow (Bastron, 1980). The fairly well preserved GFR, despite the reduced renal perfusion, might be due to modulating effects by the renin-angiotensin system (Hall et al., 1979; Levens et al., 1981). The low sodium excretion observed after burn is a common reaction found after different kinds of trauma. Earlier investigations ascribed this sodium sparing effect to redistribution of intrarenal blood flow favoring inner cortical glomeruli, having greater sodium reabsorbing capacity, at the expense of outer cortical glomeruli (Carter & Wells, 1975). There is, however, increasing evidence demonstrating adrenergic neural control of renal tubular sodium reabsorption (DiBona, 1977, 1978). Thus, increased sympathetic nerve activity causing increased sodium reabsorption probably is the main explanation for the low sodium excretion after burn.

The renal excretory function in the burned and LVP treated animals (groups C and F) was quite different with high sodium and potassium amounts in the urine. Such changes of electrolyte excretion have been described during LVP infusion in non burned animals (Kurtzman et al., 1975; Akatsuka et al., 1977; Smith et al., 1979). Increased diuresis due to vasopressin has also been reported both during

physiologic doses (Grinell et al., 1968), and pharmacologic doses (Kurtzman et al., 1975). In experiments when LVP in physiological doses was found to increase urine volume, the basal diuresis were small, indicating moderate basal antidiuresis (Grinell et al., 1968; Yesberg et al., 1973; Fejes-Tóth et al., 1977). Yesberg et al. suggested that vasopressin has a two-fold effect on water excretion - an increase in water loss by augmenting GFR, and a decrease in water loss through increased tubular water reabsorption. LVP might thus, under certain circumstances, increase urine flow by a relatively large increase of the primary urine volume due to an elevated GFR and a minor change in tubular water reabsorption. This could have been the mechanism in our study, as the mean GFR was higher in the LVP treated groups (C and F) and the pigs were not hydrated. The LVP dose given was, however, large (0.2 IU/kg/hour) so other factors might be involved.

Kurtzman et al. (1975) ascribed the diuretic effect of vasopressin in pharmacologic doses to a direct tubular effect of the hormone on the electrolyte transport. The increased GFR, sodium excretion and water diuresis might further depend on LVP-induced direct effects on renal arterioles changing the efferent to afferent vascular resistance ratio or intrarenal blood flow redistribution (Akatsuka et al., 1977). It might also be a secondary result of concentration changes of electrolytes or other osmolar factors within the renal medulla (Yesberg et al., 1973; Smith et al., 1979). In the investigation of Fejes-Tóth et al. (1977) increased intrarenal prostaglandin synthesis or increased kidney sensitivity to prostaglandins were suggested to modulate the vascular, saluretic and diuretic effects of vasopressin. Recently, the protective effects on renal function exerted by prostaglandins, has been reviewed by Kramer et al., (1981) and Schnermann & Briggs (1981). There is also substantial evidence for the manifold vasopressin - prostaglandin interactions in the regulation of renal circulation, water and electrolyte transport mechanisms (Gross et al., 1981; Handler, 1981).

Increased arterial blood pressure has also been found to increase saluresis and diuresis via increased GFR and decreased tubular reabsorption (Guyton, 1981 a). Vasopressin in high dosage inhibits the release of renin (Share, 1979), moreover, the increased blood pressure during LVP infusion reduced sympathetic nervous system activity via the baroreceptors and possibly via arterial and pulmonary artery low pressure receptors (Guyton, 1981 b). Both these systems decrease urine volume and sodium content. Thus, LVP treatment might also increase diuresis and saluresis by interacting with the above mechanisms. The complex regulation of renal circu-

lation and excretory function under LVP-treatment of burns needs further elucidation.

Renal function is often depressed after medium and large size burns and by some authors considered to be one of the major determinants of survival (Cameron & Miller-Jones, 1967). Provided burn patients react similarly to the pigs in this study, the higher diuresis and saluresis during LVP treatment after burn might be confusing in the clinical situation because urine volume is often used as one of the indicators of adequate fluid substitution. However, the close circulatory and laboratory monitoring used during burn treatment probably could counteract such possible difficulties. Moreover, if the mechanisms leading to renal failure are considered (Sevitt, 1965; Loew & Meng, 1976; Brown, 1977), the higher GFR, urine flow and blood pressure during LVP infusion found in the present investigation, should counteract the renal function derangement (IV).

The earliest change in renal excretory function in the dose response group (G), was an increase in U-potassium, which occurred with the lowest LVP dose, and then continued to increase with higher LVP doses. The increase in U-potassium excretion which began before GFR was elevated, might suggest that the transport of potassium and sodium ions is handled by separate mechanisms (Hays, 1976). Saluresis and diuresis increased progressively from the second LVP dose (0.04 IU/kg/hour), which might be explained by changed intrarenal hemodynamics leading to increased GFR and thereby a greater primary urine volume. The observations made are in accordance with earlier investigations (Yesberg et al., 1973). Such intrarenal effects might cause changes in the renal interstitial electrolyte concentration and osmolality, perpetuating water and sodium excretion, even when GFR was no longer increased. An interstitial papillary wash out could further explain the decreased U-osmolality during the two highest LVP doses. Large saluresis and diuresis have also been observed during and following LVP-treatment of bleeding oesophageal varices (Verner-sson et al., unpublished data).

The significantly lower S-creatinine in group F compared with group D after 24 hours, suggests that early burn excision during LVP infusion was beneficial for renal function in this experimental study (IV). LVP-induced intrarenal vascular effects causing increased GFR and later secondary interstitial electrolyte concentration and osmolar changes probably are the mechanisms causing the increased diuresis and saluresis.

SUMMARY AND CONCLUSION

A burn model in piglets is described. A standardized full thickness skin burn covering one third of total body surface area was inflicted, the same fluid replacement was administered to all animals and hemodynamics and renal function were monitored during 4 hours in three groups and during 24 hours in three other groups. The central hemodynamics were investigated by cardiac output measurements using a thermodilution technique, and arterial, central venous, pulmonary artery and pulmonary artery occlusion pressures were monitored and also used to calculate left ventricular work, stroke volume, systemic and coronary resistances. Regional blood flow was studied with the radioactive microsphere method, before, 2, 4 and 24 hours after the burn. Renal function was evaluated by measuring the diuresis, urinary sodium and potassium excretion and by calculating glomerular filtration rate. In the 4 hour experiments the effects of anesthesia per se were studied (group A) and the effects of the standardized burn were studied in another group (B). In a third group (C), the effects of the standardized burn and treatment with lysine-vasopressin (LVP) was investigated. Three further groups were studied during 24 hours after the standardized burn and the following regimens were compared: Conservative treatment (group D), early excision performed 5 hours after the burn (group E) and LVP-treatment combined with early excision (group F).

In conclusion, LVP-treatment in the management of experimental burn injuries has the following effects:

1. The burn injury causes an early decrease in cardiac output of approximately 30 per cent. In conservatively treated piglets the reduction of cardiac output remains for 24 hours. After excision, performed 5 hours after burn, there is a gradual recovery in cardiac output, which started after 12 hours. Lysine-vasopressin (LVP) treatment, given as a continuous infusion (0.2 IU/kg/hour), does not change the early cardiac output reaction to the burn. After excision, however, cardiac output restitution starts after 8 hours and from this time and to the end of the experiment, 24 hours after the burn, cardiac output is significantly greater in the burn-LVP-excision piglets than in the burn group.
2. There is no major cardiac output redistribution due to burn, but regional perfusion is decreased mainly in proportion to the reduction of cardiac output. LVP, however, causes redistribution of cardiac output leading to increased hepatic artery flow, decreased systemic shunting and decreased proximal

gastrointestinal, skin and carcass flow, while perfusion of the other organs is of the same order as in the other burn groups.

3. The peripheral vasoconstrictor effects exerted by LVP, and evident from the decreased skin blood flow, causes an average decrease in excisional blood loss by 65 per cent.
4. Some myocardial depression is seen early after burn whether LVP is given or not. After 24 hours, however, myocardial function is restituted in the burn-LVP-excision group, but remains depressed in the burn-excision group and deteriorates further in the conservatively treated group.

The favorable hemodynamic effects of LVP-treatment and excision in this investigation can be explained by

- a) Decreased fluid loss and decreased resorption of toxins when the burned tissue is removed.
 - b) A decrease in excisional blood loss.
 - c) The effects on circulation per se.
5. Renal function is well preserved in the LVP-treated groups, with larger saluresis and diuresis and a moderately greater glomerular filtration rate compared to the burn groups. After 24 hours, S-creatinine is lower in the burn-LVP-excision group than in the burn group, indicating a better renal function.

While no a priori analogy can be made between piglets and man with regard to the effects of LVP-treatment in early burn excision, the favorable effects on blood loss during and after excision, the earlier hemodynamic restitution and the better renal function compared with conservative treatment, makes it reasonable to suggest clinical trials.



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APPENDIX

Tables I - VI

Table I. Fractional distribution of cardiac output (CO) in per cent and organ blood flows in ml/min/100 g expressed as mean $\pm$ S.D. for the anesthesia group (A, n = 6). Baseline values are given and after 2 and 4 hours of anesthesia. Underlined figures = significant change, $p < 0.05$, from baseline. Differences between burned and vasopressin treated group (C) and anesthesia group (A), * $p < 0.05$ and ** $p < 0.01$. Derived values, preportal organs = stomach, spleen, pancreas, small and large intestines, total liver = preportal organs and a. hepatica, carcass = total activity minus all organs.

Time (hours)	0		2		4	
	CO fraction %	Flow ml/min/100 g	CO fraction %	Flow ml/min/100 g	CO fraction %	Flow ml/min/100 g
Brain	1.1 ± 0.1	45 ± 5.3	1.2 ± 0.1	48 ± 5.7	1.4 ± 0.2	54 ± 6.7
Heart	4.6 ± 0.7	136 ± 16	4.8 ± 0.9	$141 \pm 17^{**}$	4.6 ± 0.6	$129 \pm 11^{**}$
Lungs	6.0 ± 2.0	81 ± 28	<u>2.8 ± 1.9</u>	<u>38 ± 26</u>	<u>2.2 ± 1.5</u>	<u>28 ± 20</u>
Stomach	1.7 ± 0.4	21 ± 4.7	$2.0 \pm 0.8^{**}$	$24 \pm 7.9^{**}$	$1.8 \pm 0.6^{**}$	$21 \pm 4.5^{**}$
Spleen	3.3 ± 1.5	250 ± 102	2.5 ± 1.1	184 ± 65	4.0 ± 2.1	282 ± 143
Pancreas	0.7 ± 0.2	48 ± 14	$0.9 \pm 0.4^{**}$	$58 \pm 20^{**}$	$1.0 \pm 0.3^{**}$	$64 \pm 15^{**}$
Small intestine	13.4 ± 2.2	49 ± 7.0	$13.4 \pm 3.0^*$	$48 \pm 7.2^{**}$	13.1 ± 3.3	$44 \pm 3.4^{**}$
Large intestine	4.5 ± 0.7	36 ± 6.7	4.2 ± 0.7	33 ± 4.5	4.0 ± 0.4	30 ± 4.2
Preportal organs	23.5 ± 2.7		23.0 ± 3.5		23.9 ± 3.9	
A. hepatica	11.2 ± 2.8	53 ± 9.5	$13.4 \pm 2.6^{**}$	63 ± 11	$13.5 \pm 3.4^{**}$	61 ± 18
Total liver	34.7 ± 4.1	166 ± 14	$36.3 \pm 4.0^*$	171 ± 13	$37.4 \pm 3.7^{**}$	170 ± 24
Kidneys	10.2 ± 2.2	252 ± 41	11.5 ± 2.1	$284 \pm 49^{**}$	<u>13.8 ± 1.9</u>	<u>$324 \pm 51^{**}$</u>
Skin		2.0 ± 0.3		$1.8 \pm 0.2^{**}$		$2.2 \pm 0.5^{**}$
Carcass	43.4 ± 6.4	6.7 ± 1.1	$43.3 \pm 4.3^*$	$6.6 \pm 0.7^{**}$	$40.3 \pm 2.7^{**}$	$5.8 \pm 0.4^{**}$

Table II. Fractional distribution of cardiac output (CO) in per cent and organ blood flows in ml/min/100 g expressed as mean $\pm$ S.D. for the burned group (B, n = 6). Preburn values are given and also data 2 and 4 hours after burn. Underlined figures = significant change, $p < 0.05$, from preburn values. Differences between burn group (B) and anesthesia group (A), * $p < 0.05$ and ** $p < 0.01$. Derived values, preportal organs = stomach, spleen, pancreas, small and large intestines, total liver = preportal organs and a. hepatica, carcass = total activity minus all organs.

Time (hours)	0		2		4	
	CO fraction %	Flow ml/min/100 g	CO fraction %	Flow ml/min/100 g	CO fraction %	Flow ml/min/100 g
Brain	1.1 ± 0.2	45 ± 3.3	1.3 ± 0.2	44 ± 4.6	1.5 ± 0.2	$42 \pm 5.7^*$
Heart	4.4 ± 0.4	137 ± 25	4.5 ± 0.3	$112 \pm 19^*$	4.7 ± 0.5	$97 \pm 13^{**}$
Lungs	4.2 ± 1.6	60 ± 25	3.2 ± 1.6	36 ± 18	2.9 ± 1.3	28 ± 14
Stomach	1.6 ± 0.3	20 ± 4.0	2.2 ± 0.6	22 ± 6.7	1.7 ± 0.3	$14 \pm 3.2^{**}$
Spleen	2.8 ± 0.8	211 ± 62	3.3 ± 1.2	207 ± 90	4.3 ± 1.1	218 ± 58
Pancreas	0.8 ± 0.3	46 ± 12	0.7 ± 0.3	34 ± 11	$0.6 \pm 0.2^{**}$	$24 \pm 9.2^{**}$
Small intestine	12.2 ± 2.7	46 ± 13	11.6 ± 1.7	$35 \pm 6.6^*$	12.4 ± 1.9	$31 \pm 4.3^{**}$
Large intestine	5.0 ± 2.0	36 ± 11	4.7 ± 1.1	28 ± 5.7	4.5 ± 1.0	$22 \pm 3.7^*$
Preportal organs	22.3 ± 3.6		22.5 ± 3.1		23.5 ± 2.8	
A. hepatica	11.6 ± 5.6	49 ± 21	13.7 ± 5.0	48 ± 18	15.3 ± 4.0	43 ± 11
Total liver	34.0 ± 5.2	145 ± 20	36.3 ± 4.9	$126 \pm 23^{**}$	38.8 ± 3.1	$111 \pm 13^{**}$
Kidneys	10.6 ± 2.1	241 ± 45	11.8 ± 1.5	$216 \pm 17^{**}$	14.0 ± 2.0	$216 \pm 40^{**}$
Skin		3.0 ± 1.9		1.5 ± 0.4		$1.3 \pm 0.3^{**}$
Carcass	45.8 ± 8.4	7.3 ± 1.7	43.0 ± 6.0	5.5 ± 1.1	38.1 ± 3.1	$4.1 \pm 0.5^{**}$

Table III. Fractional distribution of cardiac output (CO) in per cent and organ blood flows in ml/min/100 g expressed as mean $\pm$ S.D. for the burned and LVP-treated group (C). Preburn values are given and also data 2 and 4 hours after burn. Underlined figures = significant change, $p < 0.05$, from preburn values. Differences between burn - LVP group (C) and burn group (B), * $p < 0.05$ and ** $p < 0.01$. Derived values, preportal organs = stomach, spleen, pancreas, small and large intestines, total liver = preportal organs and a. hepatica, carcass = total activity minus all organs.

Time (hours)	0		2		4	
	CO fraction %	Flow ml/min/100 g	CO fraction %	Flow ml/min/100 g	CO fraction %	Flow ml/min/100 g
Brain	1.0 ± 0.3	43 ± 11	1.5 ± 0.3	48 ± 10	1.6 ± 0.3	49 ± 6.6
Heart	4.3 ± 0.6	125 ± 18	4.7 ± 0.6	102 ± 14	4.6 ± 0.6	96 ± 13
Lungs	3.5 ± 2.2	44 ± 28	2.3 ± 1.3	22 ± 14	$1.4 \pm 0.6^{**}$	$13 \pm 5.9^*$
Stomach	1.5 ± 0.5	20 ± 6.4	$1.0 \pm 0.1^{**}$	$9.8 \pm 1.1^{**}$	$1.1 \pm 0.1^{**}$	$10 \pm 1.8^*$
Spleen	2.8 ± 1.1	192 ± 90	3.2 ± 0.9	155 ± 37	4.3 ± 1.8	203 ± 68
Pancreas	0.7 ± 0.2	40 ± 11	$0.3 \pm 0.1^*$	$11 \pm 2.7^{**}$	$0.3 \pm 0.1^*$	$11 \pm 2.1^*$
Small intestine	13.0 ± 4.2	51 ± 15	9.4 ± 1.1	$27 \pm 1.2^{**}$	$10.0 \pm 0.6^{**}$	28 ± 3.4
Large bowel	5.1 ± 1.3	38 ± 12	5.2 ± 1.2	28 ± 5.7	5.1 ± 0.7	27 ± 5.3
Preportal organs	23.0 ± 5.8		19.0 ± 2.8		20.8 ± 1.6	
A. hepatica	13.2 ± 3.4	58 ± 17	$25.8 \pm 4.7^{**}$	$84 \pm 21^*$	$26.2 \pm 2.5^{**}$	$82 \pm 14^{**}$
Total liver	36.2 ± 7.1	160 ± 42	$44.8 \pm 5.5^*$	145 ± 28	$46.9 \pm 2.8^{**}$	$147 \pm 18^{**}$
Kidneys	11.3 ± 1.3	224 ± 35	12.4 ± 1.3	$180 \pm 22^{**}$	14.6 ± 1.2	205 ± 22
Skin		1.9 ± 0.3		$0.5 \pm 0.1^{**}$		$0.6 \pm 0.2^{**}$
Carcass	43.7 ± 7.1	6.4 ± 1.1	$34.3 \pm 4.4^*$	$3.7 \pm 0.5^{**}$	$31.0 \pm 2.9^{**}$	$3.3 \pm 0.3^{**}$

Table IV. Fractional distribution of cardiac output (CO) in per cent and organ blood flows in ml/min/100 g expressed as mean $\pm$ S.D. for a burn group (D, n = 6). Measurements were performed before burn and 24 hours after burn. Underlined figures = significant change from preburn values ($p < 0.05$). Differences between burn-LVP-treatment-excision group (F) and burn group (D), * $p < 0.05$ and ** $p < 0.01$. Derived values, preportal organs = stomach, spleen, pancreas, small and large intestines, total liver = preportal organs and a. hepatica, carcass = total activity minus all organs.

Time (hours)	0			24		
	CO fraction %	Flow ml/min/100 g	CO fraction %	CO fraction %	Flow ml/min/100 g	Flow ml/min/100 g
Brain	1.0 $\pm$ 0.2	48 $\pm$ 11	<u>1.8 $\pm$ 0.5</u>	<u>1.8 $\pm$ 0.5</u>	<u>59 $\pm$ 7.3</u> *	<u>59 $\pm$ 7.3</u> *
Heart	4.5 $\pm$ 0.5	141 $\pm$ 16	3.7 $\pm$ 0.7	3.7 $\pm$ 0.7	81 $\pm$ 21	81 $\pm$ 21
Lungs	4.8 $\pm$ 1.9	65 $\pm$ 31	<u>2.8 $\pm$ 1.4</u> **	<u>2.8 $\pm$ 1.4</u> **	<u>27 $\pm$ 17</u> *	<u>27 $\pm$ 17</u> *
Stomach	1.5 $\pm$ 0.4	23 $\pm$ 8.8	1.7 $\pm$ 0.6*	1.7 $\pm$ 0.6*	18 $\pm$ 6.8	18 $\pm$ 6.8
Spleen	3.5 $\pm$ 1.8	273 $\pm$ 179	3.6 $\pm$ 1.8	3.6 $\pm$ 1.8	199 $\pm$ 109	199 $\pm$ 109
Pancreas	0.8 $\pm$ 0.3	57 $\pm$ 22	0.9 $\pm$ 0.2**	0.9 $\pm$ 0.2**	45 $\pm$ 17**	45 $\pm$ 17**
Small intestine	12.9 $\pm$ 4.0	53 $\pm$ 18	8.9 $\pm$ 2.8	8.9 $\pm$ 2.8	<u>25 $\pm$ 6.8</u>	<u>25 $\pm$ 6.8</u>
Large intestine	4.4 $\pm$ 1.2	38 $\pm$ 6.7	6.4 $\pm$ 2.5	6.4 $\pm$ 2.5	39 $\pm$ 12	39 $\pm$ 12
Preportal organs	23.0 $\pm$ 4.7		21.6 $\pm$ 5.22	21.6 $\pm$ 5.22		
A. hepatica	9.3 $\pm$ 3.6	38 $\pm$ 16	9.8 $\pm$ 1.7**	9.8 $\pm$ 1.7**	28 $\pm$ 5.9**	28 $\pm$ 5.9**
Total liver	32.4 $\pm$ 4.0	132 $\pm$ 12	31.4 $\pm$ 6.7	31.4 $\pm$ 6.7	89 $\pm$ 19**	89 $\pm$ 19**
Skin		2.4 $\pm$ 1.6			3.1 $\pm$ 2.1*	3.1 $\pm$ 2.1*
Kidneys	10.6 $\pm$ 2.0	237 $\pm$ 48	14.0 $\pm$ 2.5	14.0 $\pm$ 2.5	219 $\pm$ 43	219 $\pm$ 43
Carcass	46.8 $\pm$ 3.8	7.6 $\pm$ 1.1	46.4 $\pm$ 9.5	46.4 $\pm$ 9.5	5.3 $\pm$ 1.3	5.3 $\pm$ 1.3

Table V. Fractional distribution of cardiac output (CO) in per cent and organ blood flows in ml/min/100 g expressed as mean $\pm$ S.D. for the burn-excision group (E, n = 6). Measurements were performed before burn and 24 hours after burn. Underlined figures = significant change from preburn values ($p < 0.05$). There were no significant differences between burn-excision group (E) and burned group (D). Derived values, preportal organs = stomach, spleen, pancreas, small and large intestines, total liver = preportal organs and a. hepatica, carcass = total activity minus all organs.

Time (hours)	0			24		
	CO fraction %	Flow ml/min/100 g	CO fraction %	CO fraction %	Flow ml/min/100 g	Flow ml/min/100 g
Brain	1.1 $\pm$ 0.5	41 $\pm$ 17	1.7 $\pm$ 0.3	1.7 $\pm$ 0.3	55 $\pm$ 17	55 $\pm$ 17
Heart	4.0 $\pm$ 0.5	108 $\pm$ 28	4.1 $\pm$ 0.9	4.1 $\pm$ 0.9	96 $\pm$ 29	96 $\pm$ 29
Lungs	4.6 $\pm$ 2.2	56 $\pm$ 27	2.1 $\pm$ 0.8	2.1 $\pm$ 0.8	24 $\pm$ 21	24 $\pm$ 21
Stomach	1.2 $\pm$ 0.2	14 $\pm$ 3.2	2.1 $\pm$ 1.3	2.1 $\pm$ 1.3	20 $\pm$ 7.0	20 $\pm$ 7.0
Spleen	2.8 $\pm$ 1.2	172 $\pm$ 55	4.0 $\pm$ 1.2	4.0 $\pm$ 1.2	224 $\pm$ 81	224 $\pm$ 81
Pancreas	0.8 $\pm$ 0.2	48 $\pm$ 29	1.2 $\pm$ 0.4	1.2 $\pm$ 0.4	57 $\pm$ 17	57 $\pm$ 17
Small intestine	9.3 $\pm$ 2.3	34 $\pm$ 12	8.6 $\pm$ 1.9	8.6 $\pm$ 1.9	26 $\pm$ 4.9	26 $\pm$ 4.9
Large intestine	4.0 $\pm$ 1.0	27 $\pm$ 7.7	5.2 $\pm$ 1.8	5.2 $\pm$ 1.8	29 $\pm$ 7.6	29 $\pm$ 7.6
Preportal organs	18.1 $\pm$ 3.3		21.1 $\pm$ 5.2	21.1 $\pm$ 5.2		
A. hepatica	13.3 $\pm$ 8.3	51 $\pm$ 35	12.9 $\pm$ 4.5	12.9 $\pm$ 4.5	43 $\pm$ 15	43 $\pm$ 15
Total liver	31.4 $\pm$ 10	122 $\pm$ 50	34.0 $\pm$ 7.2	34.0 $\pm$ 7.2	111 $\pm$ 19	111 $\pm$ 19
Skin		1.5 $\pm$ 0.7			2.6 $\pm$ 1.1	2.6 $\pm$ 1.1
Kidneys	13.7 $\pm$ 3.9	260 $\pm$ 79	14.5 $\pm$ 4.2	14.5 $\pm$ 4.2	233 $\pm$ 47	233 $\pm$ 47
Carcass	45.2 $\pm$ 13	6.2 $\pm$ 2.1	43.6 $\pm$ 9.5	43.6 $\pm$ 9.5	5.5 $\pm$ 2.7	5.5 $\pm$ 2.7

Table VI. Fractional distribution of cardiac output (CO) in per cent and organ blood flows in ml/min/100 g expressed as mean $\pm$ S.D. for the burn-LVP-excision group (F, n = 6). Measurements were performed before burn and 24 hours after burn. Underlined figures = significant change from preburn values ($p < 0.05$). Differences between burn-LVP-excision group (F) and burn-excision group (E), * $p < 0.05$ and ** $p < 0.01$. Derived values, preportal organs = stomach, spleen, pancreas small and large intestines, total liver = preportal organs and a. hepatica, carcass = total activity minus all organs.

Time (hours)	0			24		
	CO fraction %	Flow ml/min/100 g		CO fraction %	Flow ml/min/100 g	
Brain	1.2 $\pm$ 0.3	47 $\pm$ 11		2.1 $\pm$ 0.5	<u>75 $\pm$ 11</u>	
Heart	4.6 $\pm$ 0.6	136 $\pm$ 26		4.2 $\pm$ 1.3	112 $\pm$ 29	
Lungs	4.0 $\pm$ 1.3	50 $\pm$ 17		0.8 $\pm$ 0.5**	<u>9.4 $\pm$ 6.8*</u>	
Stomach	1.4 $\pm$ 0.5	20 $\pm$ 5.6		0.9 $\pm$ 0.5**	<u>12 $\pm$ 1.5*</u>	
Spleen	4.5 $\pm$ 2.8	330 $\pm$ 234		3.4 $\pm$ 2.1	216 $\pm$ 132	
Pancreas	0.9 $\pm$ 0.4	48 $\pm$ 15		0.3 $\pm$ 0.1**	<u>13 $\pm$ 3.6**</u>	
Small intestine	9.3 $\pm$ 2.3	41 $\pm$ 10		<u>6.6 $\pm$ 1.2*</u>	<u>26 $\pm$ 3.9</u>	
Large intestine	4.0 $\pm$ 1.7	31 $\pm$ 9.5		4.6 $\pm$ 1.9	32 $\pm$ 7.9	
Preportal organs	20.0 $\pm$ 4.4			15.7 $\pm$ 3.5		
A. hepatica	9.2 $\pm$ 2.0	38 $\pm$ 9.8		<u>21.7 $\pm$ 3.4*</u>	<u>79 $\pm$ 16**</u>	
Total liver	29.2 $\pm$ 4.7	119 $\pm$ 25		<u>37.4 $\pm$ 4.8</u>	135 $\pm$ 23	
Skin		2.0 $\pm$ 0.4			1.3 $\pm$ 0.6*	
Kidneys	15.5 $\pm$ 6.1	331 $\pm$ 120		15.7 $\pm$ 3.2	302 $\pm$ 61	
Carcass	45.6 $\pm$ 2.5	7.1 $\pm$ 1.1		<u>39.8 $\pm$ 5.7</u>	<u>5.6 $\pm$ 1.7</u>	

I

THE EFFECTS OF LYSINE-VASOPRESSIN ON HEMODYNAMICS

DURING EARLY POST BURN PERIOD IN PIGS

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Abstract. In order to investigate the central and peripheral circulatory effects of a vasoactive drug, lysin vasopressin (LVP), in the early postburn period, 18 piglets were submitted to an experimental study. Anaesthesia was performed by thiopentone sodium as i.v. infusion and mechanically controlled ventilation via endotracheal intubation. Burn injury was brought about by heated metal stamps applied to the back and sides of the animals causing a full thickness skin burn corresponding to 32-35% of the total body surface area. Cardiac output decreased significantly after burn and so did organ blood flow, measured with radioactively labelled microspheres, especially after 4 hours. LVP-infusion did not further decrease cardiac output after burn but decreased the blood flow to the skin, carcass and proximal gastrointestinal tract. The liver perfusion was increased, while the flow in the other organs was not different from that in burned pigs not given LVP. The therapeutic implications are discussed.

The initial burn shock is characterized by hypovolemia, and decreased cardiac output and later there are severe functional disturbances and morphological lesions in parenchymatous organs. The course of the burn syndrome and its treatment has been extensively investigated both experimentally and clinically during the past decades, reviewed by Moncrief (1973), and Rudowski et al. (1976). There are, however, only few studies dealing with cardiac output distribution and these were performed in small animals. Thus in guinea pigs submitted to a large full thickness skin burn (70% of BSA), Ferguson et al. (1977) found severe cardiac output depression and organ blood flow changes similar to those found in hemorrhagic or endotoxin shock. Wetterlin & Björkman (1977) studied a 15% third degree burn in mice. One hour after burn changes similar to those noted by Ferguson et al. were found. Wetterlin reported that treatment with a potent longacting vasoconstrictor (triglycyl vasopressin), resulted in increased cardiac output and

organ blood flow from the second day post burn and a reduced 5-day mortality. He used a soluble flow indicator, ^{86}Rb , which does not permit repeated determinations of cardiac output distribution in the same animal.

The aim of the present study was to further elucidate hemodynamics, cardiac output distribution, and organ blood flow in the early post burn period with or without vasopressin infusion in pigs.

MATERIAL AND METHODS

Eighteen female piglets, weighing 24 ± 1 kg, were randomly divided into 3 experimental groups with 6 animals in each. Group A: anaesthesia (controls). Group B: standardized burn. Group C: standardized burn and treatment by lysine vasopressin (LVP).

Anaesthesia. Induction was made by Thiopentone sodium (Pentothal®, Abbott) 20 mg/kg, the animals were intubated and ventilated with 70% nitrous oxide in oxygen from an Engström 300 respirator. The ventilation volume was set to keep pCO_2 between 4.5 and 5.5 kPa. During preparation additional Pentothal was given. During a stabilization period of one hour before base line circulatory measurements were made, Pentothal infusion was given at a rate of 8 mg/kg/hour, which was then gradually reduced to 4-2 mg/kg/hour to keep a steady and superficial level of anaesthesia throughout the experiment.

Experimental procedure. A polyethylene catheter (ID 1.65 mm) was introduced into the abdominal aorta via one femoral artery for pressure recordings and blood sampling. Another catheter was placed into the left atrium through a small thoracotomy for microsphere injection according to Ericsson (1971). A Swan-Ganz flow directed thermodilution catheter (model 93 A-131-7F, Edwards Laboratories, St. Ana, Calif., USA) was introduced under fluoroscopic control into the pulmonary artery via one femoral vein. Urine sampling was made through a suprapubic cystostomy. The first circulatory measurements were made one hour after preparation was finished, and ^{103}Ru -labelled microspheres were injected. The animals in group B and C were then submitted to a standardized burn and the hemodynamics was followed during 4 hours

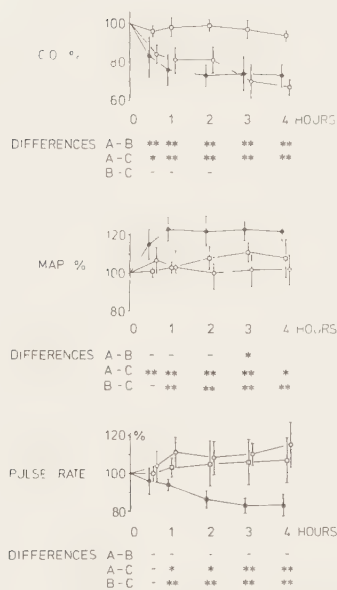


Fig. 1. Cardiac output (CO), mean arterial pressure (MAP), and pulse rate given in per cent of base line values. Anaesthesia group (A)=□, standardized burn (B)=○, and standardized burn treated by lysine vasopressin (C)=●. Differences between groups, * $p < 0.05$, and ** $p < 0.01$.

in all groups. Two hours after burn ^{141}Ce -tagged microspheres were given, and finally 2 hours later ^{46}Sc -labelled microspheres were injected. Then the animals were sacrificed and autopsied. Organs and tissues were removed, weighed and their radioactivity was measured.

Thermal injury. The pigs were submitted to a standardized full thickness skin burn (controlled by light microscopy) using metal stamps (70×100 mm), heated to 250°C, and applied to the clipped back and sides of the pig for 15 sec. The burn covered 32–35% of the total body surface area (1 stamp/kg).

Fluid therapy was the same in all groups corresponding to 2.4 ml/kg/% burn of 100 mmol NaCl/l in 2.5% glucose.

LVP-treatment. The vasopressin infusion was started 15 min after burn in group C, and continued for the rest of the experiment. The dose was 0.2 IU/kg/hour of lysine vasopressin (Postacton®, Ferring AB, Malmö, Sweden).

Pressure recordings. Mean arterial pressure (MAP), mean central venous pressure (MCVP), mean pulmonary artery pressure (MPAP), and mean pulmonary artery occlusion pressure (MPAOP) were measured using a conventional transducer (EMT-34, Siemens Elema, Stockholm, Sweden) connected with an amplifier (EMT 311 Siemens Elema) and recorded by an ink jet recorder (Mingograf 800, Siemens Elema). The reference point for

the pressure transducers was taken as a plane 5 cm dorsal to the sternal angle.

Cardiac output was determined by thermodilution technique (Gantz et al. 1971). The catheter was connected to a cardiac output computer (model 9520, Edwards Laboratories) and the thermodilution curve was also recorded by a potentiometer recorder (Servogor RE 522 S, Goertz Electro, W. Germany). As thermal indicator 5 ml of 0–1°C isotonic glucose solution was injected during 1–2 sec into the inferior caval vein during expiration. Two CO determinations were performed immediately before and 2 after the microsphere injections. When CO was measured without regional blood flow determinations, 1, 1 and 3 hours after burn, 3 separate CO readings were made. The mean of these separate determinations was taken as the actual CO.

The microspheres used, NEN-TRAC (New England Nuclear, Boston, Massachusetts, USA), measured 15 ± 1 microns in diameter, and were labelled with either ^{103}Ru , ^{141}Ce or ^{46}Sc . They were suspended in 10 ml of dextran and to prevent aggregation one drop of Tween 20 was added. Before the injection the suspension was mechanically agitated to ensure homogenous mixing, and were then given as a bolus through the catheter into the left atrium. The catheter was repeatedly flushed with saline. The radioactivity of the catheter was measured at the end of each experiment and found negligible. The number of microspheres injected ($1-2 \times 10^6$) depended on their specific radioactivity. The radioactivity given was determined as the difference between the activity of the syringes before and after the injection.

Determination of CO distribution and organ blood flow. Measurement of the distribution of CO was done according to Rudolph & Heymann (1967). Large organs were divided in pieces weighing at most 100 g. The radioactivity of all organs were measured in a Marinelli Chamber with a 4×3 inch thallium activated sodium iodide crystal placed 18 cm from the centre of the specimen. The output from the detector was transmitted to a gamma spectrometer (Canberra Analyzer 830 A, and a 816 A Multiplier), with window settings to get optimal separation of the different radionuclides; 55–190 keV (^{141}Ce), 440–580 keV (^{103}Ru), and 740–1240 keV (^{46}Sc).

Presentation of data. All results are expressed as mean $\pm$ SD. The limits for the significance of differences were determined, as appropriate, either by the Wilcoxon rank sum test or Wilcoxon's test for pair differences. p -values < 0.05 were regarded as significant.

RESULTS

The animals tolerated the experimental procedure well. There were no significant changes in MPAP, MPAOP or MCVP in any of the groups. As can be seen in Fig. 1, the hemodynamics were stable in the anaesthesia group (A). There was increased renal blood flow after 4 hours (Fig. 2). After 2 and 4 hours the lung fraction and flow was decreased.

In the burned group (B) the CO decreased significantly immediately after burn and remained low

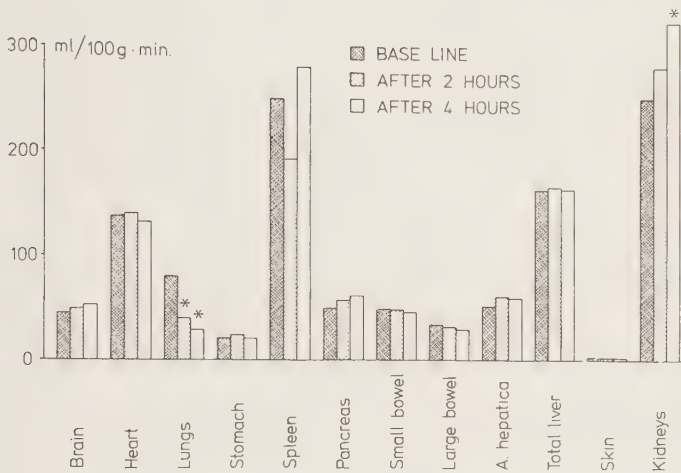


Fig. 2. Organ blood flows in the anaesthesia group, base-line values and after 2 and 4 hours. Significant change from first value. * $p < 0.05$.

throughout the experiment, while MAP and pulse rate were more stable (Fig. 1). CO was significantly lower in group B than in group A. CO fraction was unchanged to most organs but the perfusion was decreased. When group B is compared with group A, the only significant difference in CO fraction is the low pancreas fraction after 4 hours (Fig. 3). At 4 hours however, the blood flow was lower to most organs.

In the LVP-treated burned group (C), CO was reduced to the same level as in the burned group throughout the experiment (Fig. 1). Postburn there was an increase in MAP in the C group. After 1 hour it was significantly higher than in A and B (Fig. 1), and remained so during the experiment. Group C also showed a reciprocal bradycardia. In group C the CO fraction was substantially increased to the hepatic artery. The fraction was reduced to the lungs, pancreas, stomach, small bowel (4 hours), and carcass. The organ blood flow was increased to the liver, unchanged to the brain and spleen, but decreased to the other organs. When group C is compared with group B (Fig. 4), the hepatic artery fraction and flow are considerably higher in the LVP-treated group. In C both fraction and flow are lower to the lungs (4 hours), stomach, pancreas, small intestines, skin and carcass (Fig. 4).

DISCUSSION

Domestic pigs were used because they are in many ways physiologically similar to man (Bustad, 1966)

and their skin is similar to the human skin during normal conditions as well as in thermal vulnerability, and pathophysiological reactions to burn injury (Henriques & Moritz, 1947; Moritz, 1947; Wachtel et al., 1977). They are also large enough to allow of comprehensive circulatory monitoring, urine sampling and repeated blood collection without side effects. This study was performed under Pentothal- O_2/N_2O anaesthesia. To get a stable anaesthesia and to minimize the effects on circulatory parameters, the animals were normoventilated, and Pentothal was given as infusion. During the 4-hour experiment there were only minor changes in MAP, CO and pulse rate in the control group. The results indicate circulatory steady state during the experiment.

The injection of microspheres did not cause cardiac arrhythmia or changes in MAP, CO or heart rate. The microsphere technique has been shown to be valid for measuring of blood flow distribution in different animals (Rudolph & Heymann, 1967; Neutze et al., 1968; Kaihara et al., 1968; Prakash et al., 1981) and the method is well established in our laboratory (Ericsson, 1971; Ohlsson, 1971; Ahlgren et al., 1978; Rosberg & Wulff, 1979). During 4 hours of anaesthesia there was a decrease in lung fraction from 6 to 2%. This probably represents less systemic A-V shunting since most of the spheres trapped in lung capillaries originate from systemic shunts when 15 μ microspheres are used. About 1% of 50 μ spheres, which more ac-

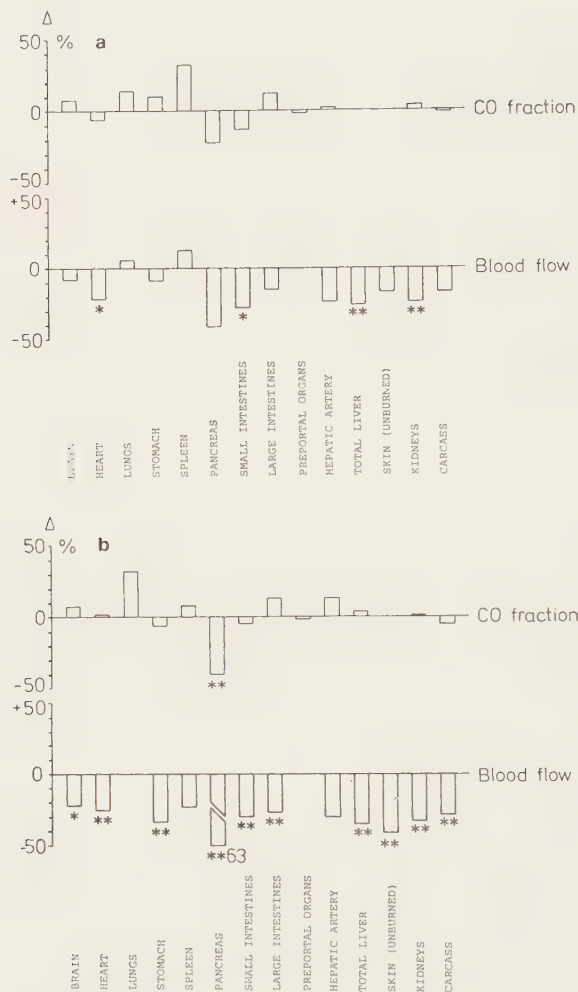


Fig. 3a and b. Differences in cardiac output fraction and organ blood flow between burned group (B) and anaesthesia group (A) after 2 (a) and 4 (b) hours respectively. * $p < 0.05$ and ** $p < 0.01$.

curately indicate bronchial artery flow, lodges in the lungs (Kaiharu et al., 1968). However the shunting of 15μ microspheres in this study, is considerably lower than in earlier reports in dogs under barbiturate anaesthesia (Kaiharu et al., 1968; Rosberg & Wulff, 1979), or in pigs receiving balanced anaesthesia (Prakash et al., 1981). The increase in the kidney fraction and flow after 4 hours, probably is a slow adaptation to long-term superficial anaesthesia, as thiopental is known to depress renal blood flow at least after induction (Sjöström &

Wulff, 1975; Gray & Nunn, 1980). In this model there was stable blood flow and CO distribution to most organs during anaesthesia, indicating that the observed changes in the B and C groups were due to the burn trauma or the treatment.

The reduction in CO, with fairly stable MAP and pulse rate observed in the burned group, is a well-known hemodynamic reaction early after burn injury (Moncrief, 1973). The severity and duration of the pathophysiologic reactions are dependent on the burned area and depth, fluid restitution and

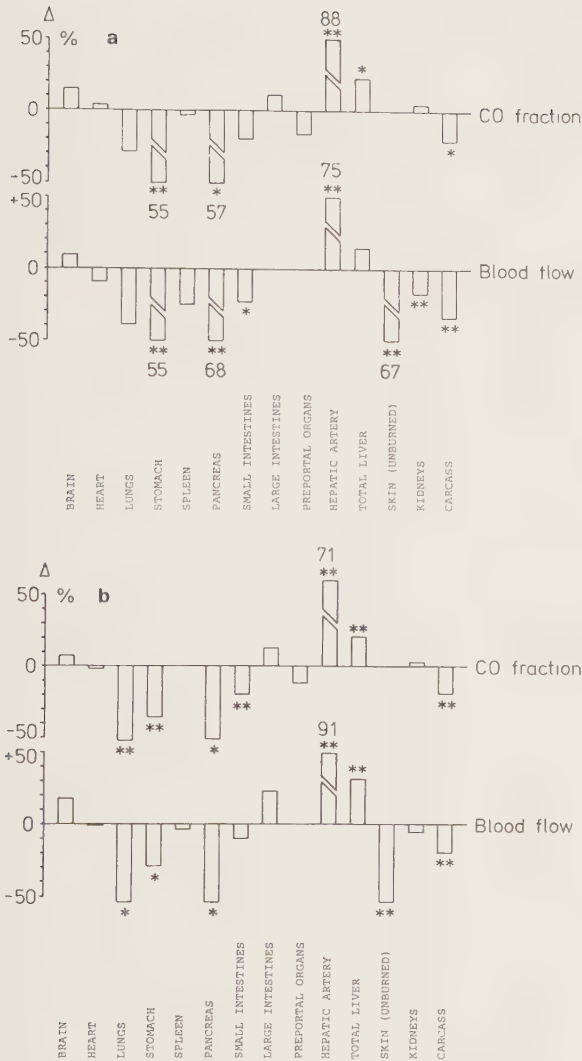


Fig. 4a and b. Differences in cardiac output fraction and organ blood flow between burned and LVP-treated group (C) and burned group (B) 2 (a) and 4 (b) hours after burn, * $p < 0.05$ and ** $p < 0.01$.

other therapy. After burn, there were only minor changes in CO distribution, and the only difference compared with the control group was a low fraction in the pancreas. In the earlier studies, Ferguson et al. (1977) and Wetterlin & Björkman, (1977) reported more pronounced CO reduction and CO redistribution. This was probably due to a more extensive burn without fluid therapy (Ferguson), less intensive fluid therapy (Wetterlin & Björkman) or

species differences. The decreased blood flow to most organs studied, can be mainly explained by reduced CO. The moderate circulatory changes observed in this investigation indicate that the fluid given was sufficient to prevent frank burn shock.

In the burned and LVP-treated animals, MAP increased and heart rate decreased, which are well-known pharmacological effects of the hormone (Drapanas et al., 1961; Corliss et al., 1968; Eric-

son, 1971). LVP-infusion after burn caused no further decrease of CO compared with the burned animals given the same fluid therapy. This would imply that hypovolemia was moderate, since LVP has been shown to increase CO in hemorrhagic hypovolemia (Ericsson, 1971) and hypovolemia due to burn (Wetterlin & Björkman, 1977), but decrease CO during normovolemia (Drapanas et al., 1961; Ericsson, 1971).

The changes in CO fraction distribution in burned pigs during LVP infusions, compared with burned animals, caused decreased systemic A-V shunting and decreased blood flow to the stomach, pancreas, small bowel (2 hours), skin, kidneys (2 hours), and carcass. The perfusion of the brain, heart, spleen, large bowel and kidneys (4 hours) was of the same order as in B, while the hepatic artery flow was greatly increased. The distribution of CO observed in this study is in accordance with earlier reports in normovolemic animals (Ericsson, 1971; Schmid et al., 1974; Cort et al., 1975), which again implies that the pigs were in a fairly good circulatory state.

LVP has been shown to decrease coronary artery flow during normovolemia, but recent investigations demonstrate a close correlation between oxygen demand and perfusion of the heart (Heyndrickx et al., 1976; Cartheuser & Komarek, 1980). In the present study the myocardial perfusion was reduced in proportion to CO, indicating no hazardous coronary artery constriction.

The large increase in hepatic artery flow induced by LVP, lead to a significantly increased total liver perfusion compared with the burned pigs, 4 hours after burn. The liver is of vital importance for the organism in preventing the development of irreversible burn shock (Arturson, 1961). Early post burn blood flow to the liver is decreased, which might interfere with its ability to eliminate toxic products (Allgöwer et al., 1973; Cuevas et al., 1974; Schoenenberger et al., 1975; Kremer et al., 1981), and to meet increased metabolic demands (Arturson, 1961). An improvement of liver perfusion after burn might be supportive for liver function.

During the last decade early excision and grafting after third degree burns has been more frequent, and has provided good clinical results (Haynes, 1969; Jancekovic, 1970; Burke et al., 1976; Quinby et al., 1981). One of the main problems during early excision of large burns is the blood loss, which can be difficult to control. In this study, LVP significantly decreased skin blood flow after burn. Studies

are in progress to evaluate whether LVP reduces blood loss during excision of burned skin.

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II

LYSINE-VASOPRESSIN IN EXCISIONAL TREATMENT OF BURNS IN PIGS

Decreased Blood Loss and Earlier Circulatory Recovery

E. Vernerissson, I. Ahlgren, K. F. Aronsen and B. Palmer

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Decreased Blood Loss and Earlier Circulatory Recovery

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Abstract. The hemodynamics were monitored during 24 hours in piglets anesthetized with Pentothal-N₂O/O₂, submitted to 33% full-thickness skin burn and resuscitated with 2.4 ml/kg/% burn of 100 mmol NaCl in 2.5% glucose. Three groups were studied: (I) standardized burn, (II) standardized burn and excision after 5 hours, (III) standardized burn, excision and lysine-vasopressin (LVP) given as intravenous infusion in a vasopressor dose. All groups showed similar decrease of cardiac output (CO), which was about 30% 4 hours after burn. In the two groups with burn excision, however, CO recovery was earlier than in the conservatively treated group I. The improvement was significant between group III and group I. LVP led to higher CO fraction and greater blood flow to hepatic artery, reduced flow to proximal gastrointestinal tract and skin and unchanged flow to heart, kidneys and other organs 24 hours after burn. The mean blood loss during and after burn excision was greatly reduced in group III (50 g/25 kg) compared with group II (146 g/25 kg). The therapeutic implications of LVP in excisional burn treatment are discussed.

In recent years, early excision and prompt grafting of third degree burns have gained wide acceptance, since this aggressive surgical approach influences the pathophysiologic events, shortens healing time and increases survival rate, at least in children (Haynes, 1969; Janzekovic, 1970; Burke, Bondoc & Quinby, 1974; MacMillan, 1978). Major blood loss is difficult to avoid, however, and may further strain an already seriously burn-injured patient.

Vasopressin, a powerful peripheral vasoconstrictor, has been found to increase cardiac output (CO) and to improve the perfusion of vital organs in hypovolemic conditions (Cort, Jeanjean, Thomson & Nickerson, 1968; Ericsson, 1971; Wetterlin & Björkman, 1977). These circulatory effects may prove favorable during early excision of burns. In a previous study on pigs, infusion of lysine-vasopressin (LVP) during the early post-burn period was

found to decrease skin blood flow without untoward effects on hemodynamics or regional blood flow (Vernerström, Ahlgren, Aronsen & Koopman, 1982). LVP in another study decreased blood loss during early excision of a standardized burn (Vernerström, Wetterlin, Ahlgren, Aronsen, Jacobsson, Opitz & Palmer, 1981).

In the present investigation, the effect of LVP on hemodynamics, CO distribution and regional blood flow was monitored during 24 hours in burned pigs. The blood loss was determined during and after burn excision, performed 5 hours after burning.

MATERIAL AND METHODS

Eighteen female piglets, weight 24 ± 2 kg, were randomly allocated to three experimental groups, each containing six animals.

Group I: Burned (controls).

Group II: Burned, with burn excision.

Group III: Burned, LVP treatment and excision.

Two additional piglets were given the standardized anesthesia during 24 hours, to observe the hemodynamic stability of the anesthesia.

Animal preparation. One week before the burn experiment, a polyethylene catheter was inserted into the left atrium through a small thoracotomy for microsphere injection according to Ericsson, under Pentothal, O₂/N₂O and Celocurine® anesthesia.

Anesthesia. Induction was made with thiopentone sodium (Pentothal®, Abbott) 20 mg/kg b w. The animals were then orotracheally intubated and ventilated with 70% nitrous oxide in oxygen from an Engström 300 respirator. The minute volume was set to maintain arterial pCO₂ between 4.5 and 5.5 kPa. During preparation, additional Pentothal was given. For a stabilisation period of 1 hour, before baseline circulatory measurements were made, Pentothal infusion was given at a rate of 8 mg/kg/hour, which was gradually reduced to 4 mg/kg/hour. After 6–8 hours the infusion rate was 2–1 mg/kg/hour, in order to maintain a steady and light anesthesia throughout the experiment.

Experimental procedure. A polyethylene catheter (ID 1.65 mm) was introduced into the abdominal aorta via a femoral artery for pressure recordings and blood sampling. A Swan-Gantz flow-directed thermodilution catheter (model 93 A-131-7 F, Edwards Laboratories, St. Ana, Calif., USA) was inserted into the pulmonary artery under fluoroscopic control via a femoral vein. Urine sampling was made through a suprapubic cystostomy. The first circulatory measurements were made 1 hour after preparation and immediately before burn, and ^{85}Sr labeled microspheres were injected into the left atrium. All animals were then submitted to a standardized third-degree burn, after which the hemodynamics were monitored for 24 hours. In groups II and III excision of the burned area was performed 5 hours after burning. At the end of the experiment, ^{45}Sc tagged microspheres were injected. The pigs were then sacrificed and autopsied. Organs and tissues were removed and weighed, and their radioactivity was measured.

Thermal injury. Standardized full-thickness skin burns were made, using metal stamps (70×100 mm) heated to 250°C and applied to the clipped back and sides of the pig for 15 seconds (1 stamp/kg b.w.). The burn covered 32–35% of the total body surface area (BSA).

Fluid supply. All the pigs received 2.4 ml/kg/% burn/24 hours. The solution was 100 mmol NaCl/l in 2.5% glucose.

LVP treatment. The vasopressin infusion was started 30 min after burn in group III and was continued throughout the experiment. The dose was 0.2 IU/kg/hour of lysine vasopressin (Postacton®, Ferring, Malmö, Sweden).

Excision. This consisted of débridement of all devitalized tissue until a freely bleeding surface was obtained. All excisions were performed by the same surgeon (B. P.), experienced in burn care. Neither surgeon nor assistant knew to which group the pigs belonged.

Blood-loss determination. At excision, bleeding vessels were clamped and the number of clamps was registered. Gauze pads were used to remove blood. During the remaining duration of the experiment, the wound surface was covered with Epigard. Blood loss was determined by weighing gauze pads and coverings before and after use. The weight of the removed tissues was also noted.

Pressure recordings. Mean arterial pressure (MAP), mean central venous pressure (MCVP), mean pulmonary artery pressure (MPAP) and mean pulmonary artery occlusion pressure (MPAOP) were measured, using a conventional pressure transducer (EMT-34), connected with an amplifier (EMT 311) and an ink jet recorder (Mingograf 800) (all apparatus from Siemens Elema, Stockholm, Sweden). The reference point for the pressure transducers was taken at a plane 5 cm dorsal to the sternal angle.

Cardiac output. Thermodilution technique was used to determine CO (Ganz, Dinso, Marcus, Forrester & Swan, 1971). The catheter was connected to a cardiac output computer (Model 9520, Edwards Laboratories) and the thermodilution curve was also recorded by a potentiometer recorder (Servogor RE 511 S, Goertz Electro, W. Germany). As thermal indicator, 5 ml of 0–1°C isotonic glucose solution was injected during 1–2 sec into the inferior vena cava during expiration. Two CO determinations were made before, and two after the microsphere

injections. When CO was measured without determination of regional blood flow, three separate readings were made. The mean of these three determinations was taken as the actual CO.

Microspheres. These (purchased from 3 M, St. Paul, Minnesota, USA) measured $15 \pm 1 \mu\text{m}$ in diameter and were labeled with either ^{85}Sr or ^{45}Sc . They were suspended in 10 ml dextran and, to prevent aggregation, a drop of Tween 20 was added to each ampoule. Before injection, the microspheres were mechanically agitated to ensure homogeneous mixing. They were then injected as a bolus through the catheter into the left atrium. The catheter was repeatedly flushed with saline solution. The radioactivity of the catheter was measured at the end of each experiment and was found to be negligible. The number of injected microspheres ($0.8\text{--}1.2 \times 10^6$) depended on their specific radioactivity. The administered radioactivity was determined as difference between the activity of the syringes before and after the injection.

Determination of CO distribution and organ blood flow. CO distribution was measured according to Rudolph & Heymann (1967). Large organs were divided into pieces weighing at most 100 g. The radioactivity of all organs was measured in a Marinelli chamber with a $4 \times 3''$ thalliumactivated sodium iodide crystal placed 18 cm from the center of the specimen. The output from the detector was transmitted to a gamma spectrometer (Canberra Analyzer 830 A with 816 A Multiplier) with window settings giving optimal separation of the different radionuclides: 440–580 keV (^{85}Sr) and 740–1240 keV (^{45}Sc).

Laboratory analyses. Blood hemoglobin and hematocrit, serum albumin and serum enzymes (alkaline phosphatase = S-ALP, aspartate-aminotransferase = S-ASAT, alanine-aminotransferase = S-ALAT and gamma glutamyl transferase = S-GT) were determined at the Department of Clinical Chemistry at Malmö General Hospital in accordance with clinical routines (Laurell, Lundh & Nosselin, 1976).

Presentation of data. All results are expressed as mean $\pm$ standard deviation. The significance of differences was determined either by the Wilcoxon rank sum test or by the Wilcoxon test for pair differences. p -values < 0.05 were regarded as significant.

RESULTS

No animals died during the experiments. The two pigs that were anesthetized but not burned had fairly stable hemodynamics (CO, MAP and pulse rate within $\pm 10\%$). In group I, CO decreased immediately after burn and tended to stabilize at 60–70% of the preburn value (Fig. 1). The heart rate was fairly stable. MAP, after an initial increase, slowly fell and leveled off at about 70% of the initial value. The blood flow was significantly increased to the brain, decreased to the heart, lungs and small bowel, but remained unchanged to the other organs (Fig. 2). A moderate but significant increase in hemo-

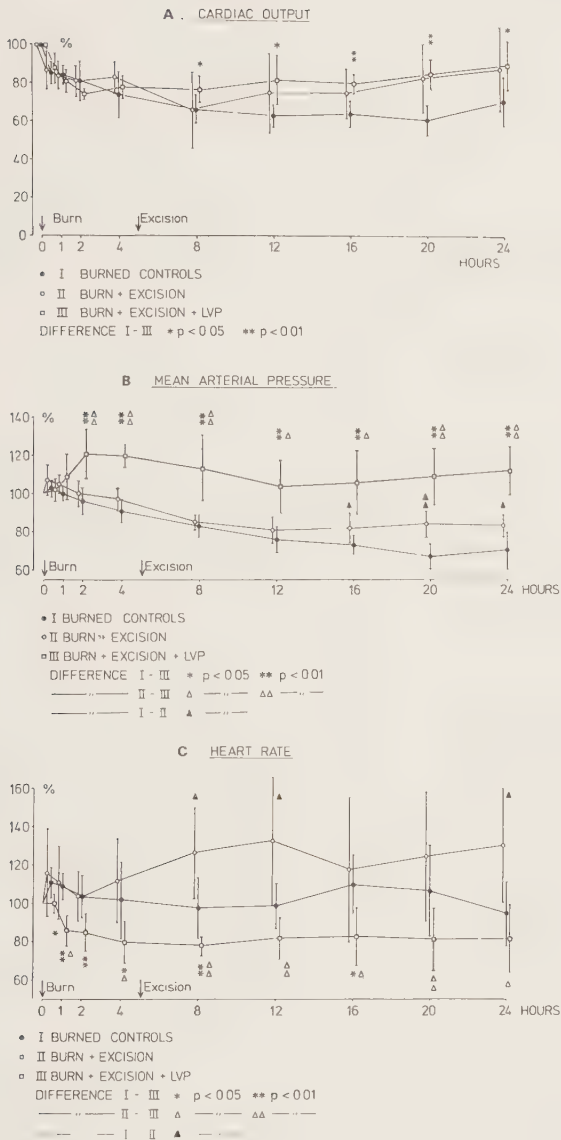


Fig. 1a, b, c. Cardiac output, mean arterial pressure and heart rate in % of preburn values (mean $\pm$ SD). $N = 6$ in all groups.

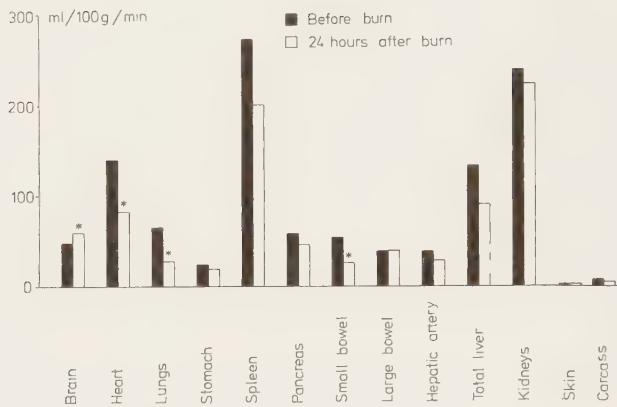


Fig. 2. Organ blood flow in group I (burn, no excision) before and 24 hours after burn. *denotes significant change from preburn values, $p < 0.05$.

globin concentration and hematocrit and a decrease in albumin could be seen 24 hours after burn (Table I). The analyzed serum enzymes showed no significant change.

In the burn-excision group (II), the initial drop in CO was the same as in the control group, but after 12 hours there was slow recovery and 88% of the preburn level was reached after 24 hours (Fig. 1). The decrease in MAP was less than in group I, and at the last three recordings MAP was significantly higher than in group I. The pulse rate was less stable in group II than in group I, and at 8, 12 and 24 hours it was significantly higher. The blood flow to the brain was increased, while the flow to the lungs was decreased and that to other organs showed only minor changes. After 24 hours there was no significant difference in organ blood flow between groups I and II. Hemoglobin, hematocrit and serum en-

zymes were fairly stable in group II (Table I), while there was moderate decrease in albumin. The blood loss during the excision was 107 ± 39 g/25 kg and after excision 39 ± 18 g/25 kg. The number of clamps used was 28 ± 8 . The weight of the excised skin and subcutaneous tissues was 1058 ± 101 g/25 kg.

In the pigs submitted to burns, LVP treatment and excision (group III), CO fell to the same level as in the other groups immediately after burn. As shown in Fig. 1, however, the recovery of CO started earlier than in the other groups, and from 8 hours after burning the CO was significantly higher in group III than in group I. It remained so throughout the observation period. LVP infusion caused increase in MAP and decrease in pulse rate (Fig. 1b, c). The blood flow in group III 24 hours after burn was increased to brain and hepatic artery, decreased

Table I. Hemoglobin concentration (Hb), hematocrit (Hcr), serum albumin (Alb) and serum enzymes before and 24 hours after burn

Figures in italics denote significant change ($p < 0.05$) from preburn value

Time(hours) ...	Group I		Group II		Group III	
	0	24	0	24	0	24
Hb (g/l)	93±12	106±21	89±15	95±17	90±13	94±11
Hcr (%)	31±4	34±6	30±6	31±7	31±2	32±4
Alb (g/l)	31±4	24±2	30±5	25±4	27±2	23±1
S-ASAT (μkat/l)	0.53±0.13	0.88±0.26	0.78±0.20	0.89±0.43	0.44±0.17	0.67±0.21
S-ALAT (μkat/l)	0.75±0.22	0.72±0.27	0.81±0.20	0.73±0.14	0.58±0.11	0.49±0.07**
S-ALP (μkat/l)	5.1±1.9	5.0±1.2	5.2±2.1	6.0±2.6	4.1±1.1	6.9±3.1
S-GT (μkat/l)	0.40±0.11	0.29±0.03	0.47±0.15	0.30±0.06	0.50±0.28	0.35±0.17

** Significantly different from group II (only significant intergroup difference).

to lungs, stomach, pancreas, small bowel and carcass, but relatively unchanged to heart, large bowel and kidneys. As compared with group I (Fig. 3), the blood flow in group III was lower to lungs, pancreas and skin, but higher to brain, hepatic artery and liver. In comparisons with group II (Fig. 3) the blood flow in group III likewise was lower to lungs, pancreas and skin. It was also lower to stomach, higher to hepatic artery and showed no significant difference to other organs.

Hemoglobin, hematocrit and albumin were fairly stable in group III (Table I). There was slight but significant increase in S-ASAT and S-ALP and minor decrease in S-ALAT and S-GT. Between the three groups there were no significant differences in these values, except for lower S-ALAT in group III than in group II. During the excision the blood loss in the LVP-treated group was 41 ± 13 g/25 kg and afterwards it was 9 ± 6 g/25 kg. The number of clamps was 22 ± 5 . The blood loss in the group with LVP treatment and excision (III) was significantly less than in the group with excision only (II). This applied to the loss during, and that after excision as well as to the total blood loss. The excised tissues weighed 1023 ± 115 g/25 kg.

DISCUSSION

The surgical principle of removing devitalized tissues has gained wide acceptance in burn care. The elimination of burn toxins by excision has been regarded as crucial to prevent impairment of host defence against infection and sepsis (Kremer, Allgöwer, Graf, Schmidt, Schoelmerich & Schoenenberger, 1981). The necrotic tissues, moreover, are excellent substrates for bacterial growth. They lead to continued loss of energy and fluid and prevent healing until they are removed and the burned area is covered with grafts (Quinby, Burke & Bondoc, 1981). The blood loss during excision has been one factor limiting this procedure. The recommendation has been made that the excised area plus the donor site should not exceed 25 to 30% of the body surface area at one operation, to avoid excessive blood loss and surgical stress (Burke, Quinby & Bondoc, 1976; Jurkiewicz, 1979). Reduction of blood loss and of operating time might permit even larger excisions in massively burned patients.

In the present study, LVP treatment significantly decreased the blood loss both during and after burn excision. This decrease can be ascribed to the

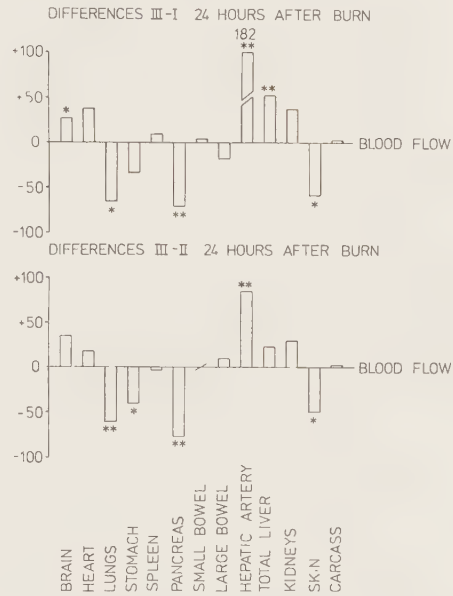


Fig. 3. Differences in organ blood flow between groups III and I and groups III and II, 24 hours after burn.

* $p < 0.05$, ** $p < 0.01$.

potent peripheral vasoconstrictor effect of high-dosage vasopressin (Ericsson; Hays, 1980; Verner-son et al., 1981; 1982).

In clinical conditions, the excisional blood loss often amounts to more than the total of the circulating blood volume when the surgical area is of the above-mentioned extent (Haynes; Levine, Salisbury, Peterson & Pruitt Jr, 1975; Burke et al., 1976). In this study on piglets, the blood loss in association with burn excision was 4 to 10% of the total blood volume. The relatively small volume of loss can be explained by the sparser skin vascularization in pig than in man (Montagna & Yun, 1964). Further, the excision was performed soon after burn, when the skin blood flow was reduced (Verner-son et al., 1982) and the burns were of uniform depth.

LVP-induced vasoconstriction in the burned area might be feared to jeopardize the survival of tissues with borderline viability and the healing of skin transplants. However, the bleeding during excision and the measured flow in adjacent skin, which increased between the 4th and the 24th hour

after burn, demonstrated maintained perfusion. The similar weight of removed tissue in the group with and that without LVP indicated that the LVP treatment did not influence the depth of the burn.

Provided that the vessels of the human skin respond to LVP in the same way (Hays) as did those of the studied pigs, substantial decrease in blood loss during burn excision may be anticipated also in humans. This concept has been confirmed by preliminary results in selected burn patients (Palmer, personal communication, 1982).

The immediate fall in CO but relatively stable MAP and pulse rate found after burn in groups I and II (without LVP) are well known early hemodynamic patterns (Moncrief, 1973). The decreased CO after burn is mainly due to loss of fluid and plasma, and myocardial depressing factors may be formed in the burned skin. The delayed CO recovery in group I may be explained by the fluid therapy (2.4 ml/kg/% burn/24 h), which is low in the range of commonly used formulas in burn resuscitation (2–4 ml/kg/% burn/24 h). Although the hemodynamics were stable in the control (anesthetized, nonburned) piglets, some depressant effects on the compensatory circulation mechanisms after burn may have been induced by light anesthesia. In the clinical situation, despite conventional management, low CO is not unusual after 24 to 48 hours (Birke, Liljedahl & Linderholm, 1958; Pruitt, Mason & Moncrief, 1971).

The excision, performed five hours after burn, did not seem to involve hazardous strain on the group II piglets. It seemed rather to promote earlier restitution of CO. This could be explained by decreased loss of fluid and terminated resorption of toxic factors when the burned tissues were removed (Kremer et al.; Quinby et al.). MAP was also higher when excision had been performed, especially after 16 hours. The hemodynamic restitution, however, was to some extent counteracted by the blood loss during burn excision. This loss was not replaced. The high pulse rate and its great variability in group II probably reflect the stress imposed on the circulatory homeostasis by the blood loss (range 54–154 g/25 kg).

In the piglets with LVP infusion, MAP was increased and the heart rate was decreased. These are well known pharmacologic effects of the hormone (Drapanas, Crowe, Shim & Schenk, 1961; Corliss, McKenna, Sialer, O'Brien & Rowe, 1968; Ericsson). The LVP treatment, started after burn, was not

associated with further postburn fall in CO as compared with the other groups. Of greater interest was the CO recovery in group III, which began after 4 hours. From 8 hours after burn, CO was significantly higher in group III than in group I, and remained so throughout the experiment.

The effect of vasopressin on CO has been shown to depend on the circulatory state before treatment. In normovolemic dogs, LVP reduces CO (Drapanas et al.; Ericsson), but observations in man were inconclusive (Erwald & Wiechel, 1978). Increased CO has been reported during LVP treatment in dogs subjected to hemorrhagic hypovolemia (Cort et al.; Ericsson) and in hypovolemic burned mice (Wetterlin & Björkman).

The favourable circulatory effect of vasopressin in shock of various kinds has been ascribed to constriction of the capacitance and mesenteric vessels, thereby increasing the central blood volume, MAP and subsequently CO (Cort et al.). LVP may, moreover, counteract hyperactivity of the sympathetic nervous system, which otherwise increases venular resistance and consequently accentuates tissue edema in decompensated shock. In our study, the CO recovery in group III did not occur until after burn excision. The moderate degree of circulatory changes indicated that, because of the administered fluid, the piglets were only moderately hypovolemic. We suggest that the mentioned CO-improving mechanisms are more important in severe hypovolemia. The more stable circulation in group III than in group II could also be partly ascribed to the reduced blood loss during excision.

In groups I and II (no LVP) there were no major changes in CO distribution, and the blood flow to most organs was decreased proportionately to the reduction of CO. Between groups I and II there were no significant differences in the measured fractions of CO. During LVP treatment (group III) the most prominent changes in CO distribution were the markedly increased hepatic artery fraction and the diminution of flow to the skin and the proximal gastrointestinal tract. The hepatic artery flow was significantly greater than in the other groups, which may imply improved liver function. The changes in regional blood flow after 24 hours were similar to those previously found early after burn (Vernerissson et al., 1982).

The changes in the analyzed serum enzymes were small in all the groups and were considered to be of little importance. Early postburn liver affect-

tion has been described in rats (Arturson, 1961) and in pigs (Levine, Ger. Stellar & Levenson, 1974). The smallness of the changes in our study may have been due to the administered fluid, containing glucose and electrolytes, and to the controlled ventilation, which ensured good oxygenation and eliminated the effort of breathing.

CONCLUSIONS

In this experimental study, LVP treatment and excision after burn contributed to hemodynamic stabilization and earlier recovery as compared with conservative management. There was also increased vascular perfusion of the liver, which may improve liver function and counteract the development of irreversible burn shock. LVP, moreover, decreased the blood flow to the skin and significantly reduced the blood loss during and after excision of burn (performed 5 hours postburn) involving 33% of the body surface area. No adverse effects of the excision-LVP regimen were found.

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III

EFFECTS OF VASOPRESSIN ON HEART FUNCTION AFTER BURN IN PIGS

Einar Vernerösson

ABSTRACT

The effects of lysine vasopressin (LVP) on cardiac function and coronary blood flow were studied in anesthetized and burned pigs. Coronary perfusion was measured with radioactive microspheres. Two and 4 hours after burn cardiac function was depressed whether LVP was given or not. After 24 hours, however, cardiac function in the LVP-treated pigs had recovered, and cardiac work was significantly higher than in the controls. LVP also led to a decreased heart rate and an increased stroke volume, especially after 24 hours. There were higher cardiac work in relation to coronary blood flow in the LVP-treated pigs, which might indicate improved cardiac efficiency. The mechanisms by which LVP might have favourable effects on heart function during burn treatment are discussed.

INTRODUCTION

Vasopressin, the antidiuretic hormone, has vasopressor effects when given in high doses. In normovolemia it also causes decrease of heart rate, cardiac output, and myocardial blood flow (Drapanas et al., 1961; Corliss et al., 1968; and Ericsson, 1971). LVP further decreases mesenteric blood flow and has been widely used to treat upper gastrointestinal bleeding (Eiseman & Norton, 1977). In experimental hypovolemia, however, vasopressin has been shown to increase cardiac output and organ blood flow (Cort et al., 1968; Ericsson, 1971; and Wetterlin & Björkman, 1977). When LVP was given to pigs early after burn, it was found that cardiac output and heart blood flow decreased to the same level as in burned controls, while skin and proximal gastrointestinal flow was further decreased, and liver perfusion was increased (Vernerissson et al., 1982 a). In another study, vasopressin treatment was shown to decrease blood loss during excision performed 5 hours post burn, and improve cardiac output, 8 - 24 hours after burn, compared with pigs treated by fluid alone (Vernerissson et al., 1982 b). There are several reports indicating cardiac arrhythmia or myocardial ischemia during LVP-treatment (Slotnik & Feigland, 1951; Drapanas et al., 1961) but later studies (Ericsson, 1971; Erwald & Wiechel, 1978), have not confirmed these untoward cardiac effects. As there are different opinions about the effects of vasopressin on cardiac performance, data from the above studies (Vernerissson et al., 1982 a,b) were worked

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through to elucidate the effects of LVP on cardiac function and coronary circulation during burn treatment.

MATERIALS AND METHODS

Thirty piglets weighing 24 ± 2 kg were used for the experiments. There were 5 groups with 6 pigs in each. All animals were submitted to a 33 % body surface area full thickness skin burn and received the same fluid therapy, corresponding to 2.4 ml/kg/% burn/24 hours of 100 mmol NaCl in 2.5 % glucose (Vernersson et al., 1982 a).

Group A. Burned and followed for 4 hours.

Group B. Burned and given synthetic lysine vasopressin (LVP, Postacton^(R), Ferring AB, Malmö, Sweden) 0.2 IU/kg/hour as continuous infusion after burn and studied for 4 hours.

Group C. Burned and followed for 24 hours.

Group D. Burned and submitted to excision 5 hours post burn and observed for 24 hours.

Group E. Burned, LVP-treated and excised 5 hours after burn and followed for 24 hours.

The pigs were given Pentothal^(R), O₂/N₂O-anesthesia, endotracheally intubated and ventilated during the whole experiment (Vernersson et al., 1982 a).

The measuring methods used are presented in detail elsewhere (Vernersson et al., 1982). The cardiac output was determined by a thermodilution technique (Ganz et al., 1971). The measurement of the distribution of CO was done by the radioactive microsphere technique according to the principles of Rudolph & Heymann (1967). All microspheres used were 15 ± 1 microns in diameter.

In group A and B the differently labelled microspheres were injected into the left atrium immediately before burn (¹⁰³Ru), 2 hours after burn (¹⁴¹Ce), and 4 hours post burn (⁴⁶Sc). In groups C, D and E the microspheres were injected before burn (⁸⁵Sr) and 24 hours after burn (⁴⁶Sc). The activity of the different isotopes in the organs were measured with the use of gamma-spectrometry. Coronary blood flow values were calculated as the cardiac output fraction to the heart of each isotope, multiplied by the mean cardiac output, determined immediately before and after the respective microsphere injection.

The heart rate was calculated from the aortic pulse recordings. The mean arterial pressure, the mean pulmonary artery occlusion pressure, and the mean central venous pressure were measured via catheters in the aorta, the pulmonary artery and the caval vein respectively.

The stroke volume was calculated by dividing values of cardiac output with heart rate. The external left ventricular work was estimated as the mean pressure gradient from the left atrium (MPAOP) to the aorta in mm Hg, multiplied by the cardiac output in l/min (Shabot, Shoemaker & State, 1977). The systemic vascular resistance was calculated as the mean pressure gradient from the aorta to the vena cava, divided by the cardiac output. Coronary vascular resistance was calculated as the mean pressure gradient from the aorta to the vena cava, divided by coronary blood flow.

Statistical comparisons were carried out either by the Wilcoxon rank sum test or Wilcoxon's test for pair differences. Differences having p-values < 0.05 were regarded as significant.

RESULTS

The used results are summarized in tables I and II, presenting mean values for each group before burn, and at 2, 4 and 24 hours after burn. Mean arterial pressure was stable early after burn (group A), but decreased after 24 hours (group C and D). In the burned and LVP-treated groups (B and C), mean arterial pressure was invariably increased. There were rather small changes in mean pulmonary artery occlusion pressure in all groups.

Cardiac output decreased significantly (33 %) 4 hours after burn (group A), and remained low during 24 hours (group C). In group B, cardiac output decreased to the same level as in group A. After excision, cardiac output almost recovered in groups D and E. Twenty-four hours after burn, the decrease in cardiac output was significantly less in the LVP-treated group (E) than in group C. After burn heart rate was fairly stable (groups A and C), increased in the excised group (D), and decreased during LVP-infusion (groups B and E). Stroke volumes were invariably decreased after burn (groups A, C and D). The decrease was moderate in group B early after burn, but in group E, 24 hours post burn, stroke volume was slightly increased and significantly higher than in groups C and D.

Table I. Hemodynamic parameters given as mean values before, 2 and 4 hours after burn. Group A was submitted to the standardized 33 % BSA burn, and group B was burned and given LVP-treatment. Percentual changes from preburn values are also presented. Underlined figures mean significant changes, $p < 0.05$, from preburn values. Differences between groups, $p < 0.05 = *$, and $p < 0.01 = **$. $N = 6$ in all groups.

		Group A	Group B
Mean arterial pressure (mm Hg)	Before	95	96
	After 2 h	95	118
	Change (%)	0	<u>+23</u> (A**)
	After 4 h	96	117
	Change (%)	+1	<u>+22</u> (A**)
Mean pulmonary artery occlusion pressure (mm Hg)	Before	8.2	9.0
	After 2 h	9.0	10.5
	Change (%)	+10	+17
	After 4 h	8.7	9.7
	Change (%)	+6	+8
Cardiac output (l/min/25 kg)	Before	3.5	3.2
	After 2 h	2.8	2.4
	Change (%)	<u>-20</u>	-25
	After 4 h	2.3	2.3
	Change (%)	<u>-33</u>	<u>-28</u>
Heart rate (beats/min)	Before	124	130
	After 2 h	133	113
	Change (%)	+7	-13 (A**)
	After 4 h	142	107
	Change (%)	+15	<u>-18</u> (A**)
Stroke volume (ml/stroke)	Before	28	25
	After 2 h	21	21
	Change (%)	<u>-25</u>	<u>-16</u>
	After 4 h	17	22
	Change (%)	<u>-39</u>	<u>-12</u> (A**)

Table I (continued)

		Group A	Group B
Left ventricular work (Watt/25 kg)	Before	$7.5 \cdot 10^{-2}$	$7.1 \cdot 10^{-2}$
	After 2 h	$6.1 \cdot 10^{-2}$	$6.3 \cdot 10^{-2}$
	Change (%)	<u>-19</u>	<u>-11</u>
	After 4 h	$5.1 \cdot 10^{-2}$	$6.2 \cdot 10^{-2}$
	Change (%)	<u>-32</u>	<u>-13</u>
Systemic vascular resistance (dyne $\cdot$ sec/cm 3)	Before	133	143
	After 2 h	166	244
	Change (%)	<u>+25</u>	<u>+71</u> (A**)
	After 4 h	201	248
	Change (%)	<u>+51</u>	<u>+73</u>
Coronary blood flow (ml/min/100 g)	Before	137	125
	After 2 h	112	102
	Change (%)	-18	<u>-19</u>
	After 4 h	97	96
	Change (%)	<u>-29</u>	<u>-23</u>
Coronary resistance	Change (%) 2 h	<u>+23</u>	<u>+51</u> (A*)
	Change (%) 4 h	<u>+42</u>	<u>+59</u>

External left ventricular work was significantly decreased after burn (groups A and C). It was also reduced in group B, but to a lesser degree. After 24 hours external left ventricular work had recovered in group E, and was significantly higher than in group C and D. In the LVP-treated groups (B and E), there were significantly higher ($p < 0.01$) external left ventricular work related to coronary blood flow, than in the other groups (A, C and D). Systemic vascular resistance increased early after burn (group A), and the increase was more pronounced during LVP-treatment (group B). After 24 hours systemic vascular resistance was unchanged in groups C and D, but moderately increased in group E. Figure 1 gives the individual values for coronary blood flow and external left ventricular work in group A, C and D, relative to preburn values. Figure 2, presents the corre-

Table II. Hemodynamic parameters given as mean values before, and 24 hours after burn, and percentual changes from preburn values. Group C was submitted to the standardized 33 % BSA burn. Group D was burned and after 5 hours excision of the burned area was performed. Group E was treated by LVP-infusion after burn and was also excised 5 hours post burn. Underlined figures mean significant changes, $p < 0.05$, from the preburn values. Differences between groups, $p < 0.05 = *$, and $p < 0.01 = **$.

	Group C			Group D			Group E		
Mean arterial pressure (mm Hg)	Before		120			116			116
	After 24 h		85			96			128
	Change (%)		<u>-29</u>			<u>-17 (C*)</u>			<u>+10 (C**,D**)</u>
Mean pulmonary artery occlusion pressure (mm Hg)	Before		11.0			8.8			10.0
	After 24 h		9.0			7.2			8.8
	Change (%)		-18			-18			-12
Cardiac output (L/min/25 kg)	Before		3.6			3.0			3.4
	After 24 h		2.5			2.6			3.1
	Change (%)		<u>-29</u>			-12			<u>-10 (C*)</u>
Heart rate (beats/min)	Before		153			119			126
	After 24 h		143			155			101
	Change (%)		-7			<u>+30</u>			<u>-20 (C**, D*)</u>
Stroke volume (ml/stroke/25 kg)	Before		24			26			28
	After 24 h		18			18			31
	Change (%)		<u>-25</u>			<u>-31</u>			<u>+11 (C**, D**)</u>

Table II (continued).

	Group C	Group D	Group E
Left ventricular work (Watt/25 kg)	Before After 24 h Change (%)	8.0*10 ⁻² 5.8*10 ⁻² <u>-27</u>	9.1*10 ⁻² 9.0*10 ⁻² -1 (C**, D*)
Systemic vascular resistance (dyne* sec*cm ³)	Before After 24 h Change (%)	161 160 -1	166 209 +26 (C*)
Coronary blood flow (ml/min/ 100 g)	Before After 24 h Change (%)	141 81 <u>-43</u>	136 112 -18 (C*)
Coronary resis- tance	Change (%)	+26	+40

sponding values in the LVP-treated groups (B and E). The correlation between the two parameters was found to be significant. As can be seen in figure 3, cardiac function was depressed early after burn whether LVP was given or not (groups A and B) but after 24 hours heart function was better in the LVP treated and excised group (E) than in the other groups (C and D).

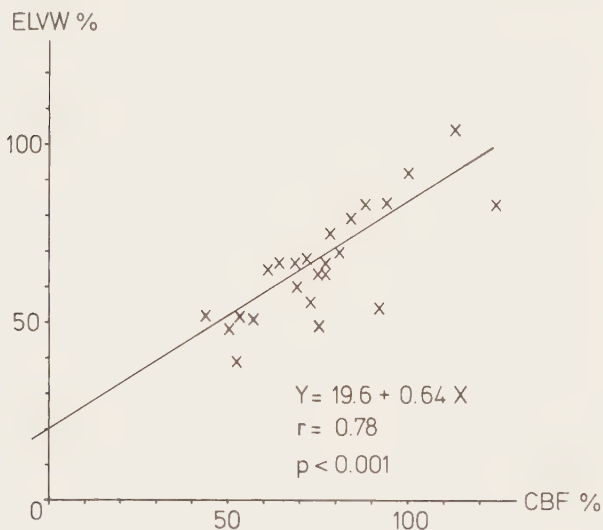


Figure 1. Individual values (group A, 2 and 4 hours after burn, group C, 24 hours post burn and the burned and excised group (D) 24 hours after burn) found for external left ventricular work (ELVW) and coronary blood flow (CBF) relative to initial values.

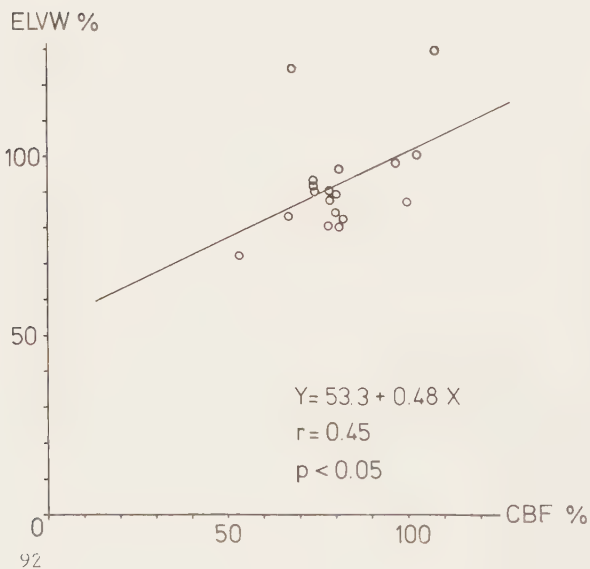


Figure 2. Individual values found for external left ventricular work (ELVW) and coronary blood flow (CBF) in the LVP-treated groups (B, 2 and 4 hours post burn, E, 24 hours after burn) relative to preburn values.

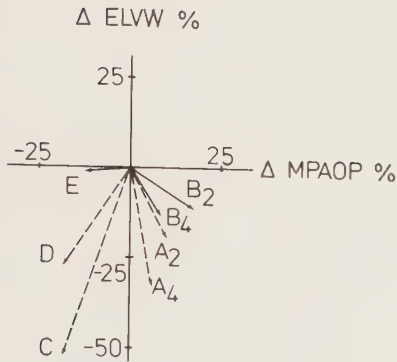


Figure 3. The relation between mean percental changes in external left ventricular work (ELVW) and mean pulmonary artery occlusion pressure (MPAOP). A = burned group and B = burned and LVP-treated group after 2 and 4 hours. C = burned group, D = burned and excised group, and E = burned, LVP-treated and excised group, 24 hours after burn.

DISCUSSION

The methods used have been discussed in detail elsewhere (Vernersson et al., 1982 a, b). When microspheres are injected into the left atrium, they are uniformly mixed with blood when leaving the heart, implying that the coronary blood flow can be measured with reliability (Kaihara et al., 1968; Domenech et al., 1969; Ericsson, 1971).

In group A, cardiac output was decreased by one third four hours after burn, due to a concomitant decrease in stroke volume. This hemodynamic change depends on the loss of plasma and fluid sequestered in the extracellular space in proportion to the extent of the burn, and is modified by the fluid and other therapy (Pruitt, Jr, Mason & Moncrief, 1971; Wachtel et al., 1977). There may also be myocardial depressant factors following large burns (Baxter et al., 1966; Moncrief, 1973). LVP-infusion early post burn did not change the decrease in cardiac output, but stroke volume was larger due to a lower heart rate (group B).

In the conservatively treated group, C, cardiac output remained low during 24 hours. This can be explained by the burn and the limited fluid volume given or there might be some depressing effects on the compensatory circulatory mechanisms after burn caused by light anesthesia, although the described anesthesia had little hemodynamic effects per se (Vernersson et al., 1982 a,b). In group D, cardiac output was preserved by an increased heart rate, while stroke volume was

substantially decreased. In the LVP-treated group (E), however, the cardiac output recovery was obtained by a moderately increased stroke volume. The cardiac output recovery in groups D and E might be explained by decreased fluid sequestration and less toxin resorption as the burned tissues were removed (Kremer et al., 1982; Quinby et al., 1981; Vernerström et al., 1982 b). In group E, LVP might also have contributed to circulatory recovery by constricting the capacitance and mesenteric vessels, and by counteracting sympathetic nervous system overactivity, which otherwise leads to venular constriction and increased fluid sequestration in decompensated shock (Cort et al., 1968). These effects by LVP increase venous return and central blood volume and thereby cardiac output. The hemodynamic effects by LVP in this study, suggests that the pigs were moderately hypovolemic due to the burn and the limited fluid volume given.

The increased vascular resistance observed early after burn (group A) can be explained by vasoconstriction due to increased sympathetic activity and to elevated blood viscosity. The results are in accordance with those found by Moncrief in dogs (1966), by Leape in monkeys (1971) and by Wetterlin in mice (1977). The vascular resistance was further increased during LVP-infusion, caused by its peripheral vasoconstrictor effects.

Early after burn the external left ventricular work was decreased mainly due to the decreased cardiac output in all groups. LVP-treatment in group B, led to an increased blood pressure and a moderately higher left ventricular work compared with group A. In the LVP-treated and excised group (E), left ventricular work had reached its preburn level after 24 hours and was significantly higher than in groups C and D. The restitution in external left ventricular work in group E was due to the recovered cardiac output and the moderate increase in mean arterial pressure.

The positive correlation between coronary blood flow and external left ventricular work observed (fig. 1 and 2) was expected, since cardiac load is the main factor determining the metabolic demands of the heart, which is the main coronary perfusion regulator (Berne, 1964). The results are in accordance with those found by Ericsson (1972) during LVP-infusion in dogs.

In the LVP-treated groups (B and E), there were, however, significantly higher external left ventricular work related to coronary blood flow compared with the other groups (A, C and D). Therefore it might be suggested that LVP improved cardiac efficiency expressed as cardiac work related to oxygen consumption.

LVP is known to decrease the metabolic demands of the heart by reflex vagal inhibition due to increased blood pressure, a negative chronotropic effect mediated via the central nervous system, and a direct depressant effect on the myocardium (Varma et al., 1969; Heyndrickx et al., 1976; Cartheuser & Komarek, 1980). The decreased coronary blood flow during LVP-infusion has also been attributed to primary coronary vasoconstriction, and by some investigators found to cause myocardial ischemia (Drapanas et al., 1961). Corliss et al. in a study (1968) also noted decreased coronary perfusion during vasopressin infusion, but found that cardiac metabolism remained aerobic, indicating that the blood supply was sufficient for the metabolic demands of the heart. The different results could be explained by very large vasopressin doses given as a bolus in the earlier investigations, and also by different experimental protocols.

Early after burn the left ventricular function (fig. 3), as reflected in changes in external left ventricular work and pulmonary artery occlusion pressure, was depressed whether LVP was given or not. These results are in accordance with those found by Baxter et al. (1966), and Raffa et al. (1978), and might be explained by myocardial depressant factors formed in burned skin and circulating in burn plasma. After 24 hours, cardiac function seemed to be best in group E and worst in group C. This could be explained by the combined favourable effects of decreased fluid loss and decreased toxin resorption after the excision, and also the effects of LVP on circulation per se. Thus, in this experimental study, the cardiac pump function and efficiency seemed to be improved by early excision of burn during LVP-treatment.



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IV

EFFECTS OF LYSINE-VASOPRESSIN TREATMENT ON RENAL FUNCTION IN BURNED PIGS

E.Vernerösson, I. Ahlgren and K.F. Aronsen

ABSTRACT

The effects of lysine-vasopressin (LVP), on renal excretory function and renal blood flow were studied in anesthetized and burned pigs either treated conservatively or by early excision 5 hours after burn. Renal perfusion was measured with radioactive microspheres. Diuresis and the urinary excretion of sodium and potassium were determined. Glomerular filtration rate (GFR) was measured either as the endogenous creatinine clearance rate or the clearance rate of ^{51}Cr -EDTA. LVP-treatment in pharmacologic doses after burn caused larger diuresis, and larger sodium and potassium excretion rates than in unburned controls and animals submitted to burn only. Renal blood flow decreased significantly early after burn whether LVP was given or not. After burn, GFR was moderately higher in the LVP-treated pigs than in the animals submitted to burn only. After 24 hours S-creatinine was lower in the pigs treated by LVP and excision of the burned tissues after 5 hours, compared with the conservatively treated animals. This implies that an active surgical approach to full thickness skin burns might support renal function. LVP-induced intrarenal effects causing increased GFR and secondary medullary interstitial electrolyte concentration and osmolar changes could be the mechanisms causing the renal functional changes found in this investigation.

INTRODUCTION

Although severe renal failure has become less frequent with increasing knowledge of burn pathophysiology and treatment, it still carries a poor prognosis and may be an associated factor in the death of many burn patients (Cameron & Miller-Jones, 1967; Ekelund, Granberg & Liljedahl, 1970; Davies et al., 1979). In several experimental studies vasopressin-treatment has been shown to increase cardiac output and the blood flow in vital organs (heart, brain, liver and kidneys) during hemorrhagic hypovolemia (Cort et al., 1968; Ericsson, 1971) and hypovolemia due to burn (Wetterlin & Björkman, 1977). In a burn model in piglets lysine-vasopressin infusion was also found to promote earlier circulatory recovery compared with animals treated only with fluid (Vernersson et al., 1982 b). Since vasopressin in pharmacologic doses is known to cause profound changes in hemodynamics and renal excretory function (Kurtzman et al., 1975;

Hays, 1980), this study was performed to investigate the effects of vasopressin treatment on renal function after burn in pigs.

MATERIAL AND METHODS

Forty-three piglets weighing 24 ± 2 kg were used. The material was divided into 7 experimental groups as follows:

Group A: Anesthesia (4 hours, $n = 6$).

Group B: Standardized burn (4 hours, $n = 6$).

Group C: Standardized burn and treatment by synthetic lysine-vasopressin. [(LVP, Postacton^(R), Ferring AB, Malmö, Sweden) 0.2 IU/kg/hour as continuous infusion throughout the experiment (4 hours, $n = 6$)].

Group D: Standardized burn (24 hours, $n = 6$).

Group E: Standardized burn submitted to excision 5 hours after burn and monitored for 24 hours, ($n = 6$).

Group F: Standardized burn, LVP-treatment and excision 5 hours post burn and followed 24 hours, ($n = 6$).

Group G: Anesthetized and given increasing doses of LVP (0, 0.008, 0.04, 0.2 and 0.4 IU/kg/hour), ($n = 7$).

The pigs were anesthetized with Pentothal^(R)-infusion, intubated and ventilated with 70 per cent N₂O in oxygen during the whole experiment (Vernersson et al., 1982 a). The animals in group B - F were submitted to a full thickness skin burn covering 33 per cent of the body surface area and in groups A - F all received the same fluid therapy, consisting of 2.4 ml/kg/% burn/24 hours, with 100 mmol NaCl in 2.5 per cent glucose (Vernersson et al., 1982 a). Group G was given 3.3 ml/kg/hour of the same solution, which was equivalent to the mean fluid infusion rate in groups D - F.

The hemodynamic measuring methods are presented elsewhere (Vernersson et al., 1982 a, b). Cardiac output was determined by a thermodilution technique (Ganz et al., 1971). Renal blood flow was determined by the radioactive microsphere technique according to Rudolph & Heymann, (1967). Carbonized microspheres 15 ± 1 microne in diameter, were used and the model presented by Vernersson et al. (1982 a).

The kidney blood flow was measured before burn and after 2 and 4 hours in groups A - C, and before burn and after 24 hours in groups D - F. Catheters were introduced into the aorta and pulmonary artery for pressure recordings and blood sampling and into the bladder for urine sampling.

Serum (S) and urine (U)-sodium concentrations and S- and U-potassium concentrations were determined by flame photometry and U-osmolality by the freezing-point depression technique (Dorwart & Chalmers, 1975). Creatinine was determined by the Jaffé reaction (Bartels & Böhmer, 1971). Glomerular filtration rate (GFR) was estimated by determining the endogenous creatinine clearance rate in groups A - F. In group G LVP was given in increasing doses, and to ensure that a new circulatory steady state was reached, 20 - 30 minutes were allowed to pass before the next sampling period. In this group (G) GFR was estimated by measuring the clearance rate of ^{51}Cr -EDTA with a continuous infusion technique for each LVP-dose. Before the first sampling period a priming dose of ^{51}Cr -EDTA (corresponding to one hour of infusion) was given and then followed by a continuous infusion. The amount of radioactivity given was 2.25 micro Curie per hour. Samples were taken at the beginning and end of each clearance period (one hour), and the ^{51}Cr -activity of the plasma was measured in an automatic well counter (2 x 2 inch well crystal, Nuclear, Chicago). The bladder was rinsed with saline immediately before each urine sampling period and completely emptied. At the end of the sampling period the bladder was rinsed again and the activity of this rinsing fluid and the urine (water added to a volume of 1.0 l) was measured in a Marinelli chamber with a 4 x 3 inch thallium activated NaI crystal. The efficiency of the well counter was 5.2 times that of the other detector. Thus GFR in ml/min was $\frac{\text{U-counts} \times 5.2}{\text{S-counts}}$. The spectral window setting was 240 - 390 keV for both detectors.

Statistical comparisons were carried out either by the Wilcoxon rank sum test or Wilcoxon's test for pair differences. Differences having p-values < 0.05 were regarded as significant.

RESULTS

Cardiac output and arterial blood pressure were stable in the anesthesia group. (A, fig. 1). After burn cardiac output decreased approximately 30 per cent whether they were treated by LVP or not (groups B - F), and remained low for 24

hours in group D. After excision in groups E and F cardiac output gradually recovered, and from 8 hours post burn, it was significantly higher in group F compared with group D (fig.2). Mean arterial pressure (MAP) was relatively stable for about 4 hours after burn in groups B, D and E, but later decreased (fig. 1 and 2). In the LVP-treated groups (C and F) MAP was invariably increased.

Renal blood flow increased during 4 hours of anesthesia, but decreased early after burn (groups B and C) and was significantly lower than in the anesthesia group (A) as can be seen in table I. The kidney blood flow was still moderately decreased 24 hours after burn, and there were no significant differences between the groups (D, E and F).

Early after burn GFR was slightly lower in group B compared with the controls (A), but in the LVP-treated group (C) GFR was significantly higher than in group B (fig.1). During the 24-hours experiments mean GFR was higher in the LVP-treated group compared with the other groups, but the difference was significant only during two periods (fig.2)

Diuresis was moderately lower after burn compared with the anesthesia group (A), but in group C it was significantly higher (fig.1). The urine volume was markedly larger in the LVP-treated group (F) than in the other groups (D and E) throughout the 24-hour study (fig.2).

In the burned groups (B, C and E) there was low urine sodium excretion (table II) compared with the A group, while the potassium excretion was higher. In the groups given LVP (C and F) the sodium and potassium excretions were markedly larger. U-osmolality was lower in group C than in group B (table II).

S-sodium remained stable in groups D, E and F during 24 hours (table III) and so did S-potassium except for a small decrease in group F. S-creatinine increased during the experiment in the burned group (D) and was unchanged in groups E and F. S-creatinine was significantly lower in group F compared with group D after 24 hours.

In the dose-response study (group G) cardiac output decreased significantly during the two highest doses of LVP (fig.3) and MAP increased. GFR was significantly increased during the LVP-infusion rates 0.04 and 0.2 IU/kg/hour, but not during the lowest (0.008) or highest (0.4) LVP doses (fig.3). The U-volume was unchanged during the lowest LVP-dose, but with increasing LVP-dose the diuresis was markedly increased. The sodium excretion was significantly increased during

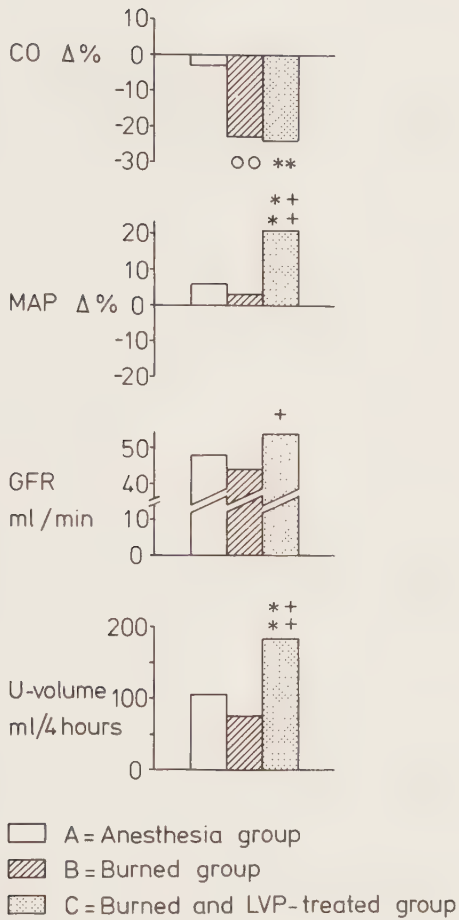


Fig.1. Mean values of changes in cardiac output (CO) and mean arterial pressure (MAP) in per cent of initial values, and mean values of glomerular filtration rate (GFR) and urine volume during 4 hours in groups A, B and C. Significant differences between group A and B, oo = $p < 0.01$, A and C, ** = $p < 0.01$, B and C + = $p < 0.05$, and ++ = $p < 0.01$.

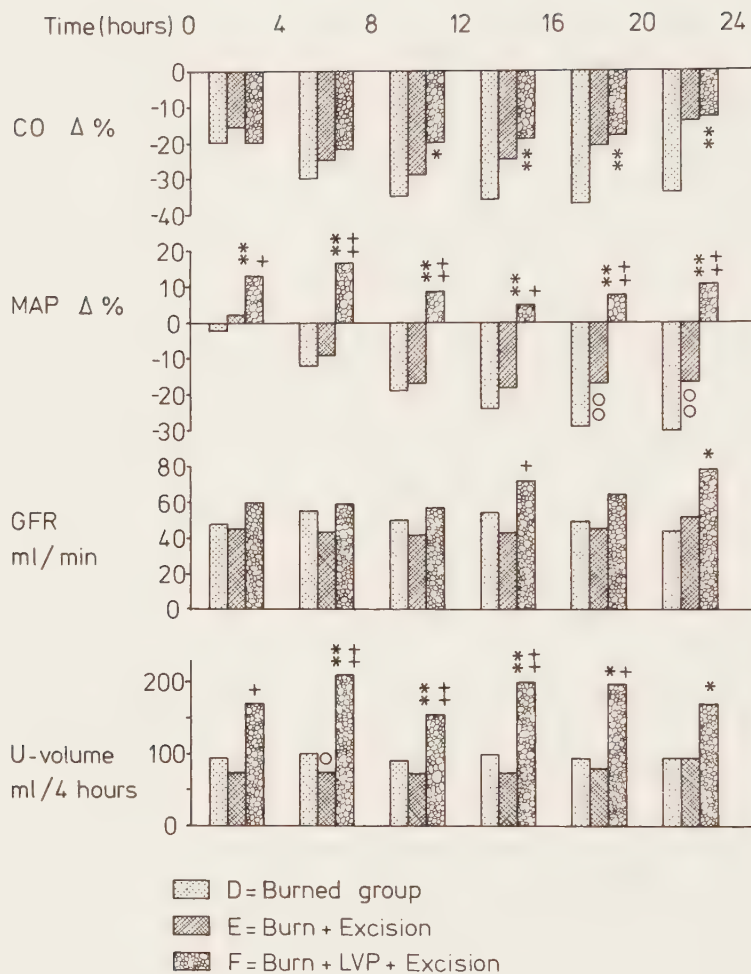


Fig.2. Mean values of changes in cardiac output (CO) and mean arterial pressure (MAP) in per cent of preburn values, and mean values of glomerular filtration rate (GFR) and urine volumes are given for each 4-hour period in the different groups. Significant differences between group D and E, o = $p < 0.05$, oo = $p < 0.01$, D and F, * = $p < 0.05$, ** = $p < 0.01$, and E and F, + = $p < 0.05$, ++ = $p < 0.01$.

Table I. Mean value $\pm$ SD for renal blood flows in the different groups. Underlined figures = significant change ($p < 0.05$) from initial values, ** = significant differences $p < 0.01$, between groups. ml/min/100 g.

Time	Group A	Group B	Group C
0	252 $\pm$ 41	241 $\pm$ 45	224 $\pm$ 35
2	284 $\pm$ 49	216 $\pm$ 17 (A**)	<u>180 $\pm$ 22</u> (A**,B**)
4	<u>324 $\pm$ 51</u>	216 $\pm$ 40 (A**)	<u>205 $\pm$ 22</u> (A**)
Time	Group D	Group E	Group F
0	237 $\pm$ 48	260 $\pm$ 79	331 $\pm$ 120
24	219 $\pm$ 43	233 $\pm$ 47	302 $\pm$ 61

Table II. Mean values $\pm$ SD for urine electrolyte excretion in groups A - F, and urine osmolality in groups A - C. Significant differences between groups, * $p < 0.05$ and ** $p < 0.01$.

	Group A	Group B	Group C
U-sodium (mmol/4 hours)	5.6 $\pm$ 2.7	2.5 $\pm$ 1.5	19.1 $\pm$ 10.6 (A**,B**)
U-potassium (mmol/4 hours)	5.0 $\pm$ 2.8	7.5 $\pm$ 4.8	15.8 $\pm$ 5.3 (A**,B**)
U-osmolality (mosm/l)	725 $\pm$ 83	806 $\pm$ 51	689 $\pm$ 75 (B*)
	Group D	Group E	Group F
U-sodium (mmol/24 hours)	4.4 $\pm$ 2.3	3.7 $\pm$ 2.7	88 $\pm$ 70 (D**,E**)
U-potassium (mmol/24 hours)	44 $\pm$ 13	42 $\pm$ 13	81 $\pm$ 48

all but the lowest LVP-dose, while the potassium excretion was increased for all doses (table IV). U-osmolality was decreased during the two highest LVP-doses. S-sodium was stable, S-potassium increased and S-creatinine decreased during the experiment (table IV).

DISCUSSION

GFR was estimated by calculating the endogenous creatinine clearance rate in the burn studies, because the method is simple, repeated 4-hour GFR values were calculated and the bladder was catheterized allowing precise urine sampling. The method has also been widely used clinically (Doolan et al., 1962). Further radioactive isotopes were used for regional blood flow measurements which might complicate the use of ^{51}Cr . In the dose response study (group G) not receiving other isotopes, ^{51}Cr -EDTA clearance was used to obtain a better accuracy (Aurell & Ditzel, 1970).

The renal function pattern early post burn (group B) with significantly lower renal blood flow and sodium excretion than in the anesthesia group (A), and fairly well preserved diuresis and GFR, has been reported in patients (O'Neill et al., 1967; Cameron & Miller-Jones, 1967). In the 24-hour experiments similar results were obtained (groups D and E). The decreased cardiac output after burn is mainly due to the plasma and fluid losses (Moncrief, 1973; Vernerissson et al., 1982 a). There may also be myocardial depressant factors formed in the burned tissues (Baxter et al., 1966). Burn trauma causes increased sympathetic nervous system activity (Arturson, 1974) which explains the decreased renal perfusion. The fairly well preserved GFR, despite the low renal blood flow might be due to modulating effects by the renin-angiotensin system, as angiotensin II preferentially constricts the efferent postglomerular arterioles causing increased filtration fraction and thereby maintaining GFR (Hall et al., 1979; Levens et al., 1981). The low sodium excretion after burn is a common reaction in trauma. This sodium sparing effect has been attributed to redistribution of intrarenal blood flow favouring inner cortical glomeruli, with greater sodium reabsorbing capacity, at the expense of outer cortical nephrons (Carter & Wells, 1975). There is, however, increasing evidence demonstrating adrenergic neural control of renal tubular sodium reabsorption, (DiBona, 1977 and 1978) and increased sympathetic nerve activity causing increased sodium reabsorption could be the main explanation for the low sodium excretion after burn.

Table III. Mean values $\pm$ SD for serum electrolytes and S-creatinine in groups D, E and F. Underlined figures = significant change $p < 0.05$ from preburn value. Significant differences between groups, * $p < 0.05$ and ** $p < 0.01$.

Time	Group D		Group E		Group F	
	0	24	0	24	0	24
S-sodium (mmol/l)	146 $\pm$ 5	144 $\pm$ 4	143 $\pm$ 3	145 $\pm$ 5	145 $\pm$ 5	141 $\pm$ 4
S-potassium (mmol/l)	4.2 $\pm$ 0.6	4.3 $\pm$ 0.3	4.0 $\pm$ 0.3	4.3 $\pm$ 0.3	4.0 $\pm$ 0.3	<u>3.8 $\pm$ 0.2 (D*, E*)</u>
S-creatinine (mmol/l)	79 $\pm$ 17	<u>106 $\pm$ 20</u>	81 $\pm$ 13	88 $\pm$ 12	77 $\pm$ 7	<u>78 $\pm$ 8 (D**)</u>

Table IV. Urine electrolytes, U-osmolality, S-electrolytes and S-creatinine (Mean $\pm$ SD) in group G for increasing LVP-doses. Underlined figures = significant change, $p < 0.05$, from baseline values.

LVP-dose (IU/kg/hour)	0	0.008	0.04	0.2	0.4
U-sodium (mmol/hour)	1.2 $\pm$ 0.6	1.2 $\pm$ 0.5	<u>4.3 $\pm$ 3.4</u>	<u>6.8 $\pm$ 5.9</u>	<u>9.1 $\pm$ 4.9</u>
U-potassium (mmol/hour)	1.3 $\pm$ 0.8	2.5 $\pm$ 1.6	<u>4.9 $\pm$ 1.3</u>	<u>7.5 $\pm$ 1.5</u>	<u>7.9 $\pm$ 2.0</u>
U-osmolality (mosm/l)	779 $\pm$ 78	798 $\pm$ 67	722 $\pm$ 87	694 $\pm$ 98	<u>696 $\pm$ 82</u>
S-sodium (mmol/l)	146 $\pm$ 4	145 $\pm$ 3	146 $\pm$ 3	145 $\pm$ 2	143 $\pm$ 3
S-potassium (mmol/l)	4.4 $\pm$ 0.4	4.5 $\pm$ 0.5	<u>4.8 $\pm$ 0.4</u>	<u>5.0 $\pm$ 0.4</u>	<u>5.1 $\pm$ 0.3</u>
S-creatinine (μ mol/l)	92 $\pm$ 10	89 $\pm$ 12	<u>86 $\pm$ 10</u>	<u>86 $\pm$ 11</u>	<u>89 $\pm$ 8</u>

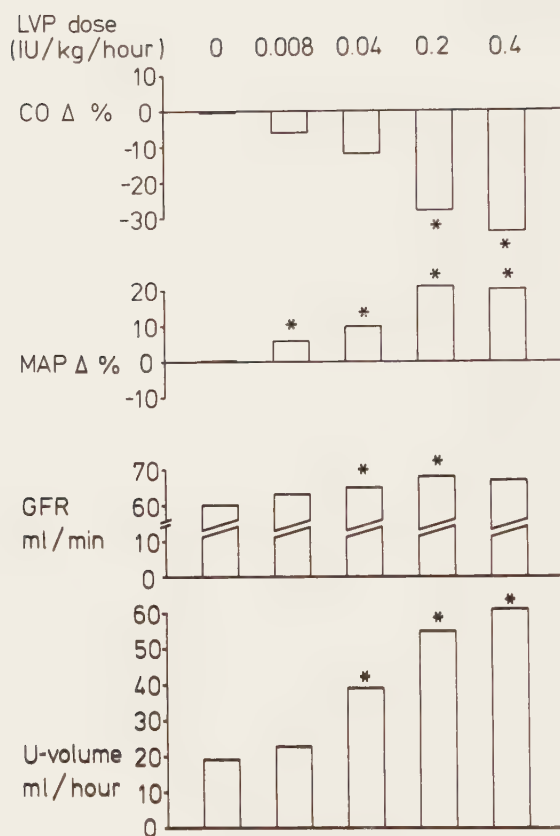


Fig.3. Mean percental changes in cardiac output (CO) and mean arterial pressure (MAP) as well as mean glomerular filtration rate (GFR) and urine volumes for the different lysine vasopressin (LVP) doses in group G. Significant change from the baseline value, * = $p < 0.05$.

The renal excretory function in the LVP-treated groups (C and F), was quite different. The high sodium and potassium excretion found in this study during LVP-infusion, is in accordance with earlier results (Kurtzman et al., 1975; Akatsuka et al., 1977; Smith et al., 1979). Increased diuresis due to vasopressin has also been reported both following low (physiologic doses (Grinell et al., 1968), and high (pharmacologic) doses (Kurtzman et al., 1975). When LVP has been found to increase urine volume in low doses, there has been a low basal urine flow, indicating moderate physiological antidiuresis (Grinell et al., 1968; Yesberg et al., 1973; Fejes-Tóth et al., 1977). The explanation suggested by Yesberg's group (1973) was that vasopressin has a two-fold effect on water excretion - an increase in water loss by augmenting GFR, and a decrease in water loss through increased tubular water reabsorption. LVP might thus increase urine flow by a relatively large increase in GFR and a minor change in tubular water reabsorption. This could have been the mechanism in our study, as the mean GFR was higher in the LVP-treated groups (C and F) and the pigs were not hydrated. The LVP-dose given (0.2 IU/kg/hour) was, however, large so other factors might be involved.

Kurtzman et al. (1975) ascribed the diuretic effect of vasopressin in pharmacological doses to a direct tubular effect of the hormone on electrolyte transport. The increased GFR, sodium excretion and water diuresis might further depend on LVP-induced direct effects on renal arterioles changing the efferent to afferent vascular resistance ratio and intrarenal blood flow redistribution or might be a secondary result of concentration changes of electrolytes or other osmolar factors within the renal interstitium (Yesberg et al., 1973; Akatsuka et al., 1977; Smith et al., 1979). In the investigation of Fejes-Tóth et al. (1977) increased intrarenal prostaglandin synthesis or increased kidney sensitivity to prostaglandins were suggested to modulate the vascular, saluretic and diuretic effects by vasopressin. Recently the protective effects on renal function exerted by prostaglandins, has been reviewed by Kramer et al. (1981) and Schnermann & Briggs (1981). There is also substantial evidence for the manifold vasopressin - prostaglandin interactions in the regulation of renal circulation, water and electrolyte transport mechanisms (Gross et al., 1981; Handler, 1981).

Increased arterial blood pressure has also been found to increase saluresis and diuresis (Guyton, 1981 a) via increased GFR and decreased tubular reabsorption. Vasopressin in high doses inhibits the release of renin (Share, 1979) and further, the increased blood pressure during LVP-infusion reduces sympathetic

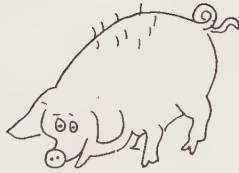
nervous system activity via the baroreceptors and possibly via arterial and pulmonary artery low pressure receptors (Guyton, 1981 b). Both these systems decrease urine volume and sodium content when activated. Thus, LVP-treatment might also increase diuresis and saluresis by interacting with the above mechanisms.

Renal function is often depressed after medium and large size burns and considered to be one of the major survival determinants (Cameron & Miller-Jones, 1967). Provided burned patients react like the pigs in this study, the higher diuresis and saluresis during LVP-treatment after burn might be confusing in the clinical situation since urine volume is often used as one of the indicators of adequate fluid resuscitation. However, the close circulatory and laboratory monitoring used during burn treatment probably could counteract such possible difficulties. Further, if the mechanisms leading to renal failure are considered (Sevitt, 1965; Loew & Meng, 1976; Brown, 1977), the higher GFR, urine flow and blood pressure during LVP-infusion in our study, should counteract renal function derangement.

In the dose-response group (G) cardiac output decreased with increasing LVP-doses, while blood pressure increased for three incremental doses but not with the highest dose. The decreased cardiac output was mainly due to a lower heart rate, and the results are in accordance with those found by Ericsson (1971). The earliest change in renal excretory function was an increase in U-potassium, which occurred with the lowest LVP-dose, and then continued to increase with higher LVP-doses. The increase in U-potassium excretion which occurred before GFR was elevated, might suggest that the transport of potassium and sodium ions is handled by separate mechanisms (Hays, 1976). Saluresis and diuresis increased progressively from the second LVP-dose (0.04 IU/kg/hour), which might be explained by changed intrarenal hemodynamics leading to increased GFR and thereby a greater primary urine volume, supporting the results of earlier studies (Yesberg et al., 1973). This might cause changes in renal interstitial electrolyte concentration and osmolality, perpetuating water and sodium excretion, even when GFR is no longer increased. An interstitial papillary wash out could also explain the decreased U-osmolality during the two highest LVP-doses. Large saluresis and diuresis have also been observed during and following LVP-treatment of bleeding oesophageal varices in some patients in our intensive care unit (Vernerissson et al., unpublished data).

The significantly lower S-creatinine in group F compared with group D after 24 hours, suggests that early burn excision during LVP-infusion was supportive

for renal function in this experimental study. LVP-induced intrarenal vascular effects causing increased GFR and later secondary interstitial electrolyte concentration and osmolar changes are suggested as the mechanisms causing increased diuresis and saluresis.



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